Visual inspection for diagnosing cutaneous melanoma in adults

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ABSTRACT

Background

Melanoma has one of the fastest rising incidence rates of any cancer. It accounts for a small percentage of skin cancer cases but is responsible for the majority of skin cancer deaths. History-taking and visual inspection of a suspicious lesion by a clinician is usually the first in a series of 'tests' to diagnose skin cancer. Establishing the accuracy of visual inspection alone is critical to understating the potential contribution of additional tests to assist in the diagnosis of melanoma.

Objectives

To determine the diagnostic accuracy of visual inspection for the detection of cutaneous invasive melanoma and atypical intraepidermal melanocytic variants in adults with limited prior testing and in those referred for further evaluation of a suspicious lesion. Studies were separated according to whether the diagnosis was recorded face-to-face (in-person) or based on remote (image-based) assessment.

Search methods

We undertook a comprehensive search of the following databases from inception up to August 2016: CENTRAL; CINAHL; CPCI; Zetoc; Science Citation Index; US National Institutes of Health Ongoing Trials Register; NIHR Clinical Research Network Portfolio Database; and the World Health Organization International Clinical Trials Registry Platform. We studied reference lists and published systematic review articles.

Selection criteria

Test accuracy studies of any design that evaluated visual inspection in adults with lesions suspicious for melanoma, compared with a reference standard of either histological confirmation or clinical follow-up. We excluded studies reporting data for 'clinical diagnosis' where dermoscopy may or may not have been used.

Data collection and analysis

Two review authors independently extracted all data using a standardised data extraction and quality assessment form (based on QUADAS-2). We contacted authors of included studies where information related to the target condition or diagnostic threshold were missing. We estimated summary sensitivities and specificities per algorithm and threshold using the bivariate hierarchical model. We investigated the impact of: in-person test interpretation; use of a purposely developed algorithm to assist diagnosis; and observer expertise.

Main results

We included 49 publications reporting on a total of 51 study cohorts with 34,351 lesions (including 2499 cases), providing 134 datasets for visual inspection. Across almost all study quality domains, the majority of study reports provided insufficient information to allow us to judge the risk of bias, while in three of four domains that we assessed we scored concerns regarding applicability of study findings as 'high'. Selective participant recruitment, lack of detail regarding the threshold for deciding on a positive test result, and lack of detail on observer expertise were particularly problematic.

Attempts to analyse studies by degree of prior testing were hampered by a lack of relevant information and by the restricted inclusion of lesions selected for biopsy or excision. Accuracy was generally much higher for in-person diagnosis compared to image-based evaluations (relative diagnostic odds ratio of 8.54, 95% CI 2.89 to 25.3, P < 0.001). Meta-analysis of in-person evaluations that could be clearly placed on the clinical pathway showed a general trade-off between sensitivity and specificity, with the highest sensitivity (92.4%, 95% CI 26.2% to 99.8%) and lowest specificity (79.7%, 95% CI 73.7% to 84.7%) observed in participants with limited prior testing (n = 3 datasets). Summary sensitivities were lower for those referred for specialist assessment but with much higher specificities (e.g. sensitivity 76.7%, 95% CI 61.7% to 87.1%) and specificity 95.7%, 95% CI 89.7% to 98.3%) for lesions selected for excision, n = 8 datasets). These differences may be related to differences in the spectrum of included lesions, differences in the definition of a positive test result, or to variations in observer expertise. We did not find clear evidence that accuracy is improved by the use of any algorithm to assist diagnosis in all settings. Attempts to examine the effect of observer expertise in melanoma diagnosis were hindered due to poor reporting.

Authors' conclusions

Visual inspection is a fundamental component of the assessment of a suspicious skin lesion; however, the evidence suggests that melanomas will be missed if visual inspection is used on its own. The evidence to support its accuracy in the range of settings in which it is used is flawed and very poorly reported. Although published algorithms do not appear to improve accuracy, there is insufficient evidence to suggest that the 'no algorithm' approach should be preferred in all settings. Despite the volume of research evaluating visual inspection, further prospective evaluation of the potential added value of using established algorithms according to the prior testing or diagnostic difficulty of lesions may be warranted.

PLAIN LANGUAGE SUMMARY

How accurate is visual inspection of skin lesions with the naked eye for diagnosis of melanoma in adults?

What is the aim of the review?

Melanoma is one of the most dangerous forms of skin cancer. The aim of this Cochrane Review was to find out how accurate checking suspicious skin lesions (lumps, bumps, wounds, scratches or grazes) with the naked eye (visual inspection) can be to diagnose melanoma (diagnostic accuracy). The Review also investigated whether diagnostic accuracy was different depending on whether the clinician was face to face with the patient (in-person visual inspection), or looked at an image of the lesion (image-based visual inspection). Cochrane researchers included 19 studies to answer this question.

Why is it important to know the diagnostic accuracy of visual examination of skin lesions suspected to be melanomas?

Not recognising a melanoma when it is present (a false-negative test result) delays surgery to remove it (excision), risking cancer spreading to other organs in the body and possibly death. Diagnosing a skin lesion (a mole or area of skin with an unusual appearance in comparison with the surrounding skin) as a melanoma when it is not (a false-positive result) may result in unnecessary surgery, further investigations, and patient anxiety. Visual inspection of suspicious skin lesions by a clinician using the naked eye is usually the first of a series of 'tests' to diagnose melanoma. Knowing the diagnostic accuracy of visual inspection alone is important to decide whether additional tests, such as a biopsy (removing a part of the lesion for examination under a microscope) are needed to improve accuracy to an acceptable level.

What did the review study?

Researchers wanted to find out the diagnostic accuracy of in-person compared with image-based visual inspection of suspicious skin lesions. Researchers also wanted to find out whether diagnostic accuracy was improved if doctors used a 'visual inspection checklist' or depending on how experienced in visual inspection they were (level of clinical expertise). They considered the diagnostic accuracy of the first visual inspection of a lesion, for example, by a general practitioner (GP), and of lesions that had been referred for further evaluation, for example, by a dermatologist (doctor specialising in skin problems).

What are the main results of the review?

Only 19 studies (17 in-person studies and 2 image-based studies) were clear whether the test was the first visual inspection of a lesion or was a visual inspection following referral (for example, when patients are referred by a GP to skin specialists for visual inspection).

First in-person visual inspection (3 studies)

The results of three studies of 1339 suspicious skin lesions suggest that in a group of 1000 lesions, of which 90 (9%) actually are melanoma:

- An estimated 268 will have a visual inspection result indicating melanoma is present. Of these, 185 will not be melanoma and will result in an unnecessary biopsy (false-positive results).

- An estimated 732 will have a visual inspection result indicating that melanoma is not present. Of these, seven will actually have melanoma and would not be sent for biopsy (false-negative results).

Two further studies restricted to 4228 suspicious skin lesions that were all selected to be excised found similar results.

In-person visual inspection after referral, all lesions selected to be excised (8 studies)

The results of eight studies of 5331 suspicious skin lesions suggest that in a group of 1000 lesions, of which 90 (9%) actually are melanoma:

- An estimated 108 will have a visual inspection result indicating melanoma is present, and of these, 39 will not be melanoma and will result in an unnecessary biopsy (false-positive results).

- Of the 892 lesions with a visual inspection result indicating that melanoma is not present, 21 will actually be melanoma and would not be sent for biopsy (false-negative results).

Overall, the number of false-positive results (diagnosing a skin lesion as a melanoma when it is not) was observed to be higher and the number of false-negative results (not recognising a melanoma when it is present) lower for first visual inspections of suspicious skin lesions compared to visual inspection following referral.

Visual inspection of images of suspicious skin lesions (2 studies)

Accuracy was much lower for visual inspection of images of lesions compared to visual inspection in person.

Value of visual inspection checklists

There was no evidence that use of a visual inspection checklist or the level of clinical expertise changed diagnostic accuracy.

How reliable are the results of the studies of this review?

The majority of included studies diagnosed melanoma by lesion biopsy and confirmed that melanoma was not present by biopsy or by follow-up over time to make sure the skin lesion remained negative for melanoma. In these studies, biopsy, clinical follow-up, or specialist clinician diagnosis were the reference standards (means of establishing final diagnoses). Biopsy or follow-up are likely to have been reliable methods for deciding whether patients really had melanoma. In a few studies, experts diagnosed the absence of melanoma

(expert diagnosis), which is less likely to have been a reliable method for deciding whether patients really had melanoma. There was lots of variation in the results of the studies in this review and the studies did not always describe fully the methods they used, which made it difficult to assess their reliability.

Who do the results of this review apply to?

Thirteen studies were undertaken in Europe (68%), with the remainder undertaken in Asia (n = 1), Oceania (n = 4), and North America (n = 1). Mean age ranged from 30 to 73.6 years (reported in 10 studies). The percentage of individuals with melanoma ranged between 4% and 20% in first visualised lesions and between 1% and 50% in studies of referred lesions. In the majority of studies, the lesions were unlikely to be representative of the range of those seen in practice, for example, only including skin lesions of a certain size or with a specific appearance. In addition, variation in the expertise of clinicians performing visual inspection and in the definition used to decide whether or not melanoma was present across studies makes it unclear as to how visual inspection should be carried out and by whom in order to achieve the accuracy observed in studies.

What are the implications of this review?

Error rates from visual inspection are too high for it to be relied upon alone. Although not evaluated in this review, other technologies need to be used to ensure accurate diagnosis of skin cancer. There is considerable variation and uncertainty about the diagnostic accuracy of visual inspection alone for the diagnosis of melanoma. There is no evidence to suggest that visual inspection checklists reliably improve the diagnostic accuracy of visual inspection, so recommendations cannot be made about when they should be used. Despite the existence of numerous research studies, further, well-reported studies assessing the diagnostic accuracy of visual inspection with and without visual inspection checklists and by clinicians with different levels of expertise are needed.

How up-to-date is this review?

The review authors searched for and used studies published up to August 2016.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Question	**What is the diagnostic accuracy of visual inspection for the detection of cutaneous invasive melanoma and atypical intraepidermalmelanocytic variants in adults?**			
Population	Adults with lesions suspicious for melanoma, including: • those with limited prior testing (presenting in primary, community or private dermatology settings) • referred populations (presenting in secondary care or specialist skin cancer clinics)			
Index test	Visual inspection with or without the use of any established algorithms or checklist to aid diagnosis, including: • in-person evaluations (face-to-face diagnosis) • image-based evaluations (diagnosis based on assessment of a clinical image)			
Target condition	Cutaneous invasive melanoma and atypical intraepidermal melanocytic variants			
Reference standard	Histology with or without long-term follow-up			
Action	If accurate, positive results ensure melanoma lesions are not missed but are appropriately referred and excised and those with negative results can be safely reassured and discharged			
		Number of studies	**Total lesions**	**Total cases**
Quantity of evidence		49[a]	34,351	2499
Limitations				
Risk of bias	Potential risk for participant selection from case-control design (6), inappropriate exclusion criteria (7) or lack of detail (27/49) All index test interpretation was blinded to reference standard diagnosis. Index test thresholds not clearly pre-specified (22/33 in-person evaluations; 13/16 image-based) Low risk for reference standard (42/49); high concern from use of expert diagnosis (6). Blinding of reference standard to visual inspection diagnosis not reported in any study High risk for participant flow due to differential verification (11), and exclusions following recruitment (15); 37 studies did not mention timing of tests			
Applicability of evidence to question	Participant selection restricted to those with melanocytic lesions only (10), or to those with histopathology results (37) and included multiple lesions per participant (14) No description of index test diagnostic thresholds (24 in-person; 13 image-based) or reporting of average or consensus diagnoses (7 in-person; 13 image-based) Clinical images interpreted blinded to clinical information (11/16). Little information given concerning the expertise of the histopathologist (40/49)			

Findings						
37 studies (providing 39 datasets) reported accuracy data for the primary target condition. We separated them a priori into in-person (n = 28) and image-based (n = 11) evaluations. Subsequent analysis confirmed differences in accuracy according to the different approaches to diagnosis (P < 0.001). Attempts to analyse studies by degree of prior testing were hampered by a lack of relevant information provided in the study publications and by the inclusion of lesions selected for biopsy or excision. Of the 28 in-person evaluations, we could only clearly place 17 on the clinical pathway, and considered 11 to have provided insufficient information to allow us to identify the pathway (coded 'unclear' on pathway). The findings presented are based on results for in-person evaluations that could be clearly placed on the clinical pathway						
Test:	**In-person visual inspection using any or no algorithm at any threshold**					
Data:				**Number of datasets**	**Total lesions**	**Total melanomas**
All in-person evaluations				28	25,604	1748
Studies clearly placed on the clinical pathway				17	14,700	622
Place on pathway: participants with limited prior testing (all lesions)						
Datasets (n)	**Lesions (n)**	**Melanomas (n)**	**Sensitivity (95% CI)**		**Specificity (95% CI)**	
3	1339	55	92% (26 to 100)		80% (74 to 85)	
Numbers in a cohort of 1000 lesions[b]	**TP**	**FP**	**FN**	**TN**	**PPV**	**NPV**
At a prevalence of 4%	37 (10 to 40)	195 (252 to 147)	3 (30 to 0)	765 (708 to 813)	16% (4 to 21)	100% (96 to 100)
At a prevalence of 9%	83 (24 to 90)	185 (239 to 139)	7 (66 to 0)	725 (671 to 771)	31% (9 to 39)	99% (91 to 100)
At a prevalence of 16%	148 (42 to 160)	171 (221 to 129)	12 (118 to 0)	669 (619 to 711)	46% (16 to 55)	98% (84 to 100)
Place on pathway: participants with limited prior testing (only lesions selected for excision)						

Datasets (n)	Lesions (n)	Melanomas (n)	Sensitivity (95% CI)		Specificity (95% CI)	
2	4228	160	90% (70 to 97)		81% (67 to 90)	
Numbers in a cohort of 1000 lesions[b]	**TP**	**FP**	**FN**	**TN**	**PPV**	**NPV**
At a prevalence of 4%	36 (28 to 39)	180 (312 to 96)	4 (12 to 1)	780 (648 to 864)	17% (8 to 29)	99% (98 to 100)
At a prevalence of 9%	81 (63 to 88)	170 (296 to 91)	9 (27 to 2)	740 (614 to 819)	32% (18 to 49)	99% (96 to 100)
At a prevalence of 16%	144 (112 to 156)	157 (273 to 84)	16 (48 to 4)	683 (567 to 756)	48% (29 to 65)	98% (92 to 99)
Place on pathway: referred participants (all lesions)						
Datasets (n)	**Lesions (n)**	**Melanomas (n)**	**Sensitivity (95% CI)**		**Specificity (95% CI)**	
2	3494	61	75% (49 to 90)		99% (95 to 100)	
Numbers in a cohort of 1000 lesions[b]	**TP**	**FP**	**FN**	**TN**	**PPV**	**NPV**
At a prevalence of 4%	30 (20 to 36)	13 (51 to 4)	10 (20 to 4)	947 (909 to 956)	69% (28 to 90)	99% (98 to 100)
At a prevalence of 9%	67 (44 to 81)	13 (48 to 4)	23 (46 to 9)	897 (862 to 906)	84% (48 to 96)	98% (95 to 99)
At a prevalence of 16%	119 (78 to 144)	12 (45 to 3)	41 (82 to 16)	828 (795 to 837)	91% (64 to 98)	95% (91 to 98)
Referred participants (only lesions selected for excision)						

Datasets (n)	Lesions (n)	Melanomas (n)	Sensitivity (95% CI)		Specificity (95% CI)	
8	5331	258	77% (62 to 87)		96% (90 to 98)	
Numbers in a cohort of 1000 lesions[b]	**TP**	**FP**	**FN**	**TN**	**PPV**	**NPV**
At a prevalence of 4%	31 (25 to 35)	41 (99 to 16)	9 (15 to 5)	919 (861 to 944)	43% (20 to 68)	99% (98 to 99)
At a prevalence of 9%	69 (56 to 78)	39 (94 to 15)	21 (34 to 12)	871 (816 to 895)	64% (37 to 84)	98% (96 to 99)
At a prevalence of 16%	123 (99 to 139)	36 (87 to 14)	37 (61 to 21)	804 (753 to 826)	77% (53 to 91)	96% (92 to 98)
Referred participants with equivocal lesions (only lesions selected for excision)						
Datasets (n)	**Lesions (n)**	**Melanomas (n)**	**Sensitivity (95% CI)**		**Specificity (95% CI)**	
2	930	88	85% (56 to 96)		89% (79 to 95)	
Numbers in a cohort of 1000 lesions[b]	**TP**	**FP**	**FN**	**TN**	**PPV**	**NPV**
At a prevalence of 4%	34 (22 to 38)	101 (197 to 48)	6 (18 to 2)	859 (763 to 912)	25% (10 to 44)	99% (98 to 100)
At a prevalence of 9%	76 (50 to 86)	96 (187 to 46)	14 (40 to 4)	814 (723 to 865)	44% (21 to 66)	98% (95 to 100)
At a prevalence of 16%	136 (89 to 154)	88 (172 to 42)	24 (71 to 6)	752 (668 to 798)	61% (34 to 79)	97% (90 to 99)

CI: confidence interval; **FN**: false-negative; **FP**: false-positive; **NPV**: negative predictive value; **PPV**: positive predictive value; **TN**: true negative; **TP**: true positive

[a]37 of the 49 included studies (reporting on 39 cohorts of lesions) provide data for the primary target condition (defined as detection of cutaneous invasive melanoma and atypical intraepidermal melanocytic variants) and are the main focus of this 'Summary of findings' table; the summary of methodological quality is based on the full sample of 49 studies.

[b]We estimated number of true positives (TP), false-positives (FP), false-negatives (FN) and true negatives (TN) for a hypothetical cohort of 1000 lesions at the median and interquartile ranges of prevalence (25th and 75th percentiles), at average sensitivity and specificity and using the lower and upper limits of the 95% confidence intervals, denoted in brackets (lower limit to upper limit).

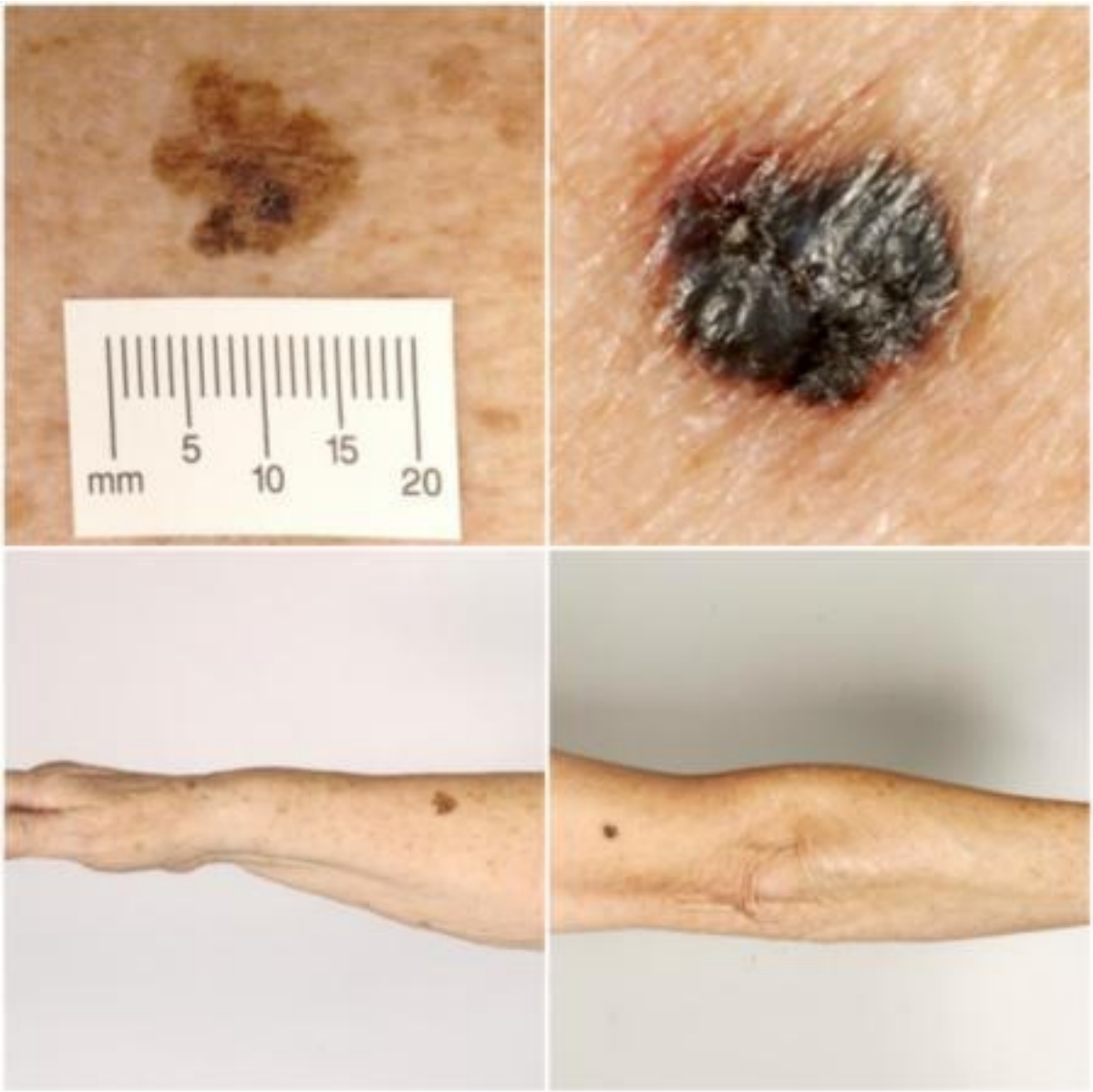
BACKGROUND

This review is one of a series of Cochrane Diagnostic Test Accuracy (DTA) reviews on the diagnosis and staging of melanoma and keratinocyte skin cancers conducted for the National Institute for Health Research (NIHR) Cochrane Systematic Reviews Programme. Appendix 1 shows the content and structure of the programme. Appendix 2 provides a glossary of terms used, and a table of acronyms used is provided in Appendix 3.

Target condition being diagnosed

Melanoma is one of the most aggressive forms of skin cancer, with the potential to metastasise to other parts of the body via the lymphatic system and blood stream. It accounts for a small percentage of skin cancer cases but is responsible for up to 75% of skin cancer deaths (Boring 1994; Cancer Research UK 2017). Melanoma arises from uncontrolled proliferation of melanocytes, the epidermal cells that produce pigment or melanin. It most commonly arises in the skin but can occur in any organ that contains melanocytes, including mucosal surfaces, the back of the eye, and lining around the spinal cord and brain. Cutaneous melanoma refers to a skin lesion with malignant melanocytes present in the dermis, and includes superficial spreading, nodular, acral lentiginous, and lentigo maligna melanoma variants (see Figure 1). Melanoma in situ refers to malignant melanocytes that are contained within the epidermis and have not yet invaded the dermis, but are at risk of progression to melanoma if left untreated. Lentigo maligna, a subtype of melanoma-in-situ in chronically sun-damaged skin, denotes another form of proliferation of abnormal melanocytes. Lentigo maligna can progress to invasive melanoma if its growth breaches the dermo-epidermal junction during a vertical growth phase (when it becomes known as 'lentigo maligna melanoma'); however, its rate of malignant transformation is both lower and slower than for melanoma in situ (Kasprzak 2015). Melanoma in situ and lentigo maligna are both atypical intraepidermal melanocytic variants.

Figure 1. Sample photographs of superficial spreading melanoma (left) and nodular melanoma (right). Copyright © 2010 Dr Rubeta Matin: reproduced with permission.



The incidence of melanoma rose to over 200,000 newly diagnosed cases worldwide in 2012 (Erdmann 2013; Ferlay 2015), with an estimated 55,000 deaths (Ferlay 2015). The highest incidence is observed in Australia with 13,134 new cases of melanoma of the skin in 2014 (ACIM 2017) and in New Zealand with 2341 registered cases in 2010 (HPA and MelNet NZ 2014). For 2014 in the USA, the predicted incidence was 73,870 per annum and the predicted number of deaths was 9940 (Siegel 2015). The highest rates in Europe are seen in north-western Europe and the Scandinavian countries, with a highest incidence reported in Switzerland: 25.8 per 100,000 in 2012. Rates in England have tripled from 4.6 and 6.0 per 100,000 in men and women, respectively, in 1990, to 18.6 and 19.6 per 100,000 in 2012 (EUCAN 2012). In the UK, melanoma has one of the fastest rising incidence rates of any cancer and has the biggest projected increase in incidence between 2007 and 2030 (Mistry 2011). In the decade leading up to 2013, age-standardised incidence increased by 46%, with 14,500 new cases in 2013 and 2459 deaths in 2014 (Cancer Research UK 2017). While overall incidence rates are higher in women than in men, the rate of incidence in men is increasing faster than in women (Arnold 2014).

The rising incidence in melanoma is thought to be primarily related to an increase in recreational sun exposure and use of tanning beds, and an increasingly ageing population with higher lifetime ultraviolet (UV) exposure, in conjunction with possible earlier detection (Belbasis 2016; Linos 2009). Putative risk factors are reviewed in detail elsewhere (Belbasis 2016), but can be broadly divided into host or environmental factors. Host factors include fair skin and light hair or eye colour; older age (Geller 2002); male sex (Geller 2002); previous skin cancer (Tucker 1985); predisposing skin lesions, for example, high melanocytic naevus counts (Gandini 2005), clinically atypical naevi (Gandini 2005), or large congenital naevi (Swerdlow 1995); genetically inherited skin disorders, for example, xeroderma pigmentosum (Lehmann 2011); and a family history of melanoma (Gandini 2005). Environmental factors include recreational, occupational, and work-related exposure to sunlight (both cumulative and episodic burning) (Armstrong 2017; Gandini 2005); artificial tanning (Boniol 2012); and immunosuppression, for example, in organ transplant recipients or HIV-positive individuals (DePry 2011). Lower socioeconomic class may be associated with delayed presentation and thus more advanced disease at diagnosis (Reyes-Ortiz 2006).

A database of over 40,000 US patients from 1998 onwards, which assisted the development of the Eighth Edition American Joint Committee on Cancer (AJCC) Staging System indicated a five-year survival of 99% for stage IA melanoma (melanoma $\leq$ 1 mm thick without ulceration, mitosis or involvement of the lymph nodes), dropping to anything between 32% and 93% in stage III disease (melanoma of any thickness with metastasis to the lymph nodes) depending on tumour thickness, the presence of ulceration and number of involved nodes (Gershenwald 2017). Before the advent of targeted and immuno-therapies, stage IV melanoma (melanoma disseminated to distant sites/visceral organs) was associated with median survival of six to nine months, one-year survival rate of 25%, and three-year survival of 15% (Balch 2009; Korn 2008).

Between 1975 and 2010, five-year relative survival for melanoma (i.e. not including deaths from other causes) in the USA increased from 80% to 94%, with survival for localised, regional, and distant disease estimated at 99%, 70%, and 18%, respectively in 2010 (Cho 2014). Overall, mortality rates however showed little change, at 2.1 per 100,000 deaths in 1975 and 2.7 per 100,000 in 2010 (Cho 2014). Increasing incidence in localised disease over the same period (from 5.7 to 21 per 100,000) suggests that much of the observed improvement in survival may be due to earlier detection and heightened vigilance (Cho 2014). New targeted therapies for stage IV melanoma (e.g. BRAF inhibitors) have improved survival and immunotherapies are evolving such that long-term survival is being documented (Pasquali 2018). No new data regarding the survival prospects for people with stage IV disease were analysed for the AJCC Eighth Edition Staging Guidelines due to lack of contemporary data (Gershenwald 2017).

Treatment of melanoma

For primary melanoma, the mainstay of definitive treatment is early detection and excision of the lesion, to remove both the tumour and any malignant cells that might have spread into the surrounding skin (Garbe 2016; Marsden 2010; NICE 2015a; SIGN 2017; Sladden 2009). Recommended surgical margins vary according to tumour thickness (Garbe 2016) and stage of disease at presentation (NICE 2015a).

Index test(s)

For the purposes of our series of reviews, each component of the diagnostic process, including visual inspection or clinical examination, is considered a diagnostic or index 'test', the accuracy of which can be established in comparison with a reference standard of diagnosis, either alone or in combination with other available technologies that may assist the diagnostic process.

Clinical history-taking to identify risk factors and visual inspection of the lesion, surrounding skin and comparison with other lesions on the rest of the body is fundamental to the diagnosis of skin cancer. The strongest common phenotypic risk factor is the presence of atypical naevi; typically the presence of over a hundred moles or naevi of abnormal appearance that may pose diagnostic challenges (Goodson 2010; Rademaker 2010; Salerni 2012). In the UK, clinical examination is typically done at two decision points - first in the general practice (GP) surgery, where a decision is made to refer or not to refer, and then a second time by a der-

matologist or other secondary care clinician, where a decision is made to biopsy or not. Specialist advice can also be sought using teledermatology, where lesion images are forwarded with variable clinical information (such as age, gender, and location of lesion) to specialist clinics or to commercial organisations for interpretation. The accuracy of these diagnostic encounters (defined as the proportion of 'correct' diagnoses, i.e. true positive plus true negative diagnoses out of the total number of diagnoses) is known to vary according to qualifications and experience (Morton 1998; Westerhoff 2000); the accuracy of 'image-based' as opposed to face-to-face diagnosis is less clear.

Research into the cognitive processes involved in dermatological diagnoses suggests that two main strategies are employed simultaneously and iteratively (Elstein 2002; Norman 1989; Norman 2009). Non-analytical pattern recognition formulates an initial hypothesis; identification is made implicitly, without conscious thought or reference to specific rules and hidden from the conscious view of the diagnostician (Norman 2009). Analytical pattern recognition, using more explicit rules based on conscious analytical reasoning, is then employed to test the initial hypothesis. Analytical pattern recognition has been described as the "careful and systematic gathering of data and weighing the elicited information against mental rules" (Norman 2009). The balance between non-analytical and analytical reasoning varies between clinicians, according to factors such as experience and familiarity with the diagnostic question.

Various attempts have been made to formalise the 'mental rules' involved in analytical pattern recognition for melanoma, ranging from setting out criteria that should be considered (e.g. 'pattern analysis'; Friedman 1985; Sober 1979) to formal scoring systems with explicit numerical thresholds (MacKie 1985; MacKie 1990). The most commonly used algorithms are described in detail in Appendix 4.

The ABCD (**a**symmetry, **b**order irregularity, **c**olour variegation, **d**iameter > 6 mm) algorithm of clinical warning signs was developed in 1985 to help distinguish melanoma from a benign naevus (Friedman 1985), and then extended to include an E for 'enlargement' criterion (Thomas 1998). As a result of its simplicity, ABCD(E) is now widely advocated for use by non-experts or lay persons (American Academy of Dermatology 2015). The approach has been criticised for its inability to capture nodular and amelanotic melanomas, which account for a relatively small proportion (~15% to 20%) of incident melanomas but a large proportion (~50%) of melanoma-related deaths (Moreau 2013; Shaikh 2012). In addition, up to a third of melanomas may be smaller than 6 mm in diameter (Maley 2014), a proportion which is likely to increase due to improved skin surveillance. The validity of ABCD(E) as a useful tool for the lay public has also been called into question (Aldridge 2011a; Girardi 2006; Liu 2005). Subsequent modifications have been suggested, including altering the meaning of the ABCD acronym for use in paediatric populations (Cordoro 2013); changing 'D' to 'dark' (Goldsmith 2014)); or changing the acronym altogether (e.g. CCC for **c**olour, **c**ontour, and **c**hange (Moynihan 1994); or "Do UC" the melanoma for **d**ifferent, **u**neven, **c**hanging (Yagerman 2014)). To date, the latter three have not been evaluated in populations with lesions suggestive for melanoma.

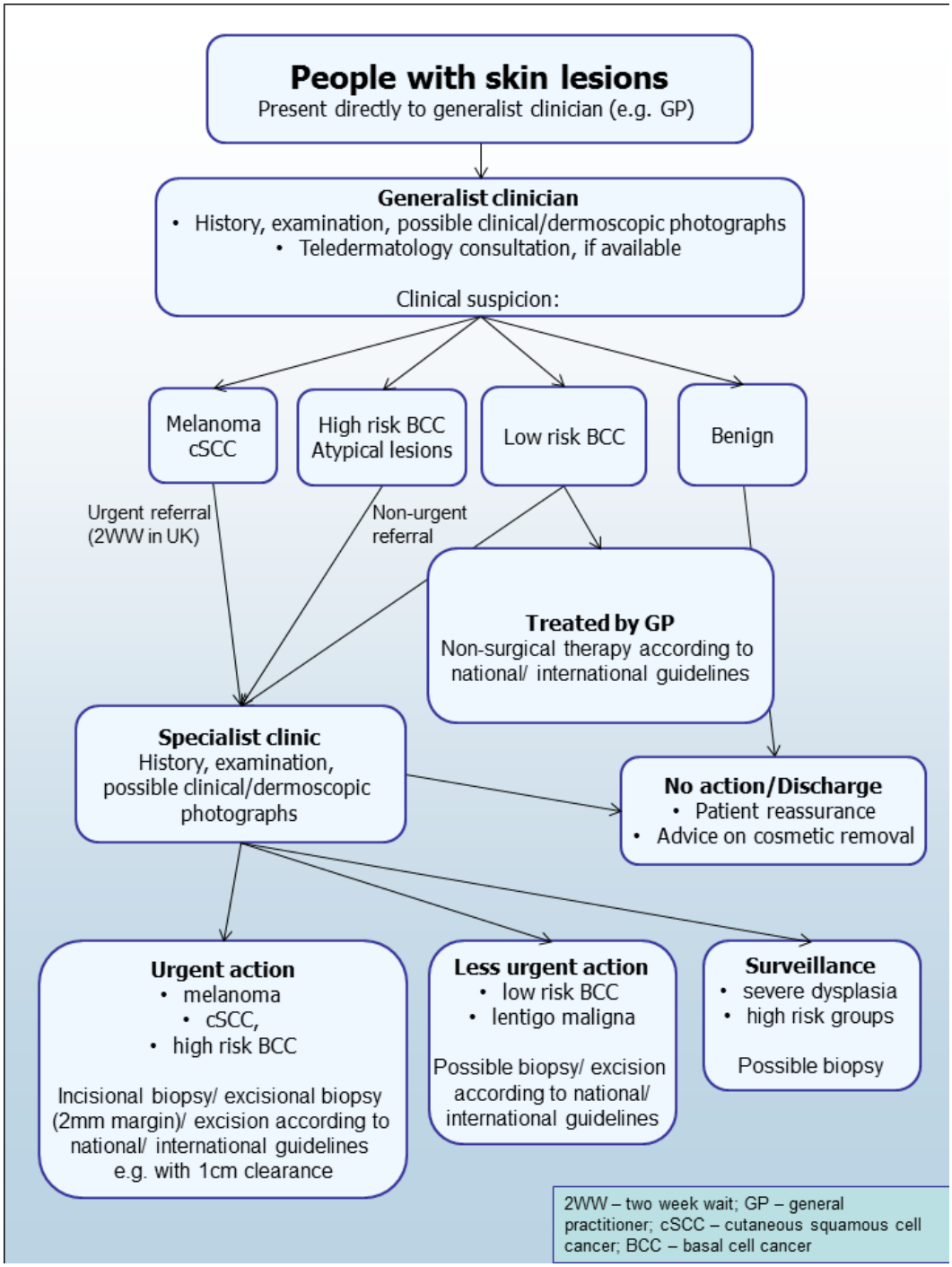
The seven-point checklist assessing change in size, shape, colour, inflammation, crusting or bleeding, sensory change, or diameter of 7 mm or more was developed by UK researchers as a guide to help non-dermatologists detect possible melanoma (MacKie 1985; MacKie 1990). The revised, weighted version (MacKie 1990), is currently recommended for GP use in the evaluation of pigmented lesions (NICE 2015a). A primary care-based evaluation found moderately good performance for the identification of clinically significant lesions (including malignant and premalignant lesions as disease-positive) in primary care (sensitivity and specificity for the presence of at least three features were 62.7% and 65.0%, respectively), with higher sensitivity for the detection of melanoma (80.6%) at the expense of low specificity (61.7%) (Walter 2013).

Unlike most formalised rules, the 'ugly duckling' sign is based on differential pattern recognition, where abnormal lesion identification is achieved by noticing the odd one out, that is, a melanoma will be the pigmented lesion that does not match the rest of a person's naevi, for example a very dark or pale/pink lesion that is different in colour compared to the rest of the pigmented naevi (Grob 1998). Although 'ugly duckling' is inherently a form of subjective pattern recognition, sensitivity has been reported to be 100% for pigmented-lesion experts and 85% for non-clinicians (Scope 2008). The assumption that an individual has a "normal" naevus phenotype is debatable, however. Many individuals have multiple 'atypical' pigmented lesions which, although very similar morphologically, allow malignancy to easily disguise itself amidst an abnormal complex of pigmented lesions (also referred to as 'The Little Red Riding Hood' phenomenon) (Mascaro 1998).

Clinical pathway

The diagnosis of melanoma can take place in primary, secondary, and tertiary care settings by both generalist and specialist healthcare providers. In the UK, people with concerns about a new or changing lesion will usually present first to their GP or, less commonly, directly to a specialist in secondary care, which could include a dermatologist, plastic surgeon, general surgeon or other specialist surgeon (such as an ear, nose, and throat (ENT) specialist or maxillofacial surgeon), or ophthalmologist (Figure 2). Current UK guidelines recommend that all suspicious pigmented lesions presenting in primary care should be assessed by taking a clinical history and visual inspection using the seven-point checklist (MacKie 1990); lesions suspected to be melanoma should be referred urgently for appropriate specialist assessment within two weeks (Chao 2013; Marsden 2010; NICE 2015b; SIGN 2017).

Figure 2. Current clinical pathway for people with skin lesions.



Teledermatology consultations can aid more appropriate triage of lesions into urgent referral; non-urgent secondary care referral (e.g. for suspected basal cell carcinoma (BCC)); or where available, referral to an intermediate care setting, for example, clinics run by GPs with a special interest in dermatology. The distinction between setting and examiner qualifications and experience is important as specialist clinicians might work in primary care settings (for example, in the UK, GPs with a special interest in dermatology and skin surgery who have undergone appropriate training), and generalists might practice in secondary care settings (for example, plastic surgeons who do not specialise in skin cancer). The level of skill and experience in skin cancer diagnosis will vary for both generalist and specialist care providers and will also impact on test accuracy.

The specialist clinician will also use history-taking and visual inspection of the lesion (in comparison with other lesions on the skin), usually in conjunction with dermoscopic examination, to inform a clinical decision. If melanoma is suspected, then urgent excision biopsy is recommended; for suspected cutaneous squamous cell carcinoma (cSCC) urgent excision with predetermined surgical margins. Other lesions such as BCC or pre-malignant lesions such as lentigo maligna may also be referred for a diagnostic biopsy, followed by appropriate treatment or further surveillance or reassurance and discharge.

Prior test(s)

Although smartphone applications and community-based teledermatology services can increasingly be directly accessed by people who have concerns about a skin lesion (Chuchu 2018), visual inspection of a suspicious lesion by a clinician is usually the first in a series of tests to diagnose skin cancer. In the UK first visual inspection of a suspicious lesion usually takes place in primary care; however, in some countries, people with suspicious lesions can present directly to a secondary care setting. Considering the degree of prior testing that study participants have undergone is key to interpretation of resulting test accuracy indices, which are known to vary according to the spectrum or case-mix of included participants (Lachs 1992; Leeflang 2013; Moons 1997; Usher-Smith 2016). Studies of people with suspicious lesions at the initial clinical presentation stage ('test-naïve'), are likely to have a wider range of differential diagnoses and include a higher proportion of people with benign diagnoses compared with studies of participants who have been referred for a specialist opinion on the basis of visual inspection (with or without dermoscopy) by a generalist practitioner. Furthermore, studies in more specialist settings may focus on equivocal or difficult-to-diagnose lesions, rather than lesions with a more general level of clinical suspicion. A simple categorisation of studies according to primary, secondary, or specialist setting may not always adequately reflect differences in spectrum.

Role of index test(s)

Visual inspection and history-taking are key to diagnosing skin cancer and are always undertaken as part of a clinical examination regardless of examiner experience and whatever additional technologies are available. For the generalist practitioner, the key is to minimise the proportion of people who are referred unnecessarily and identify those lesions that require urgent referral. For the specialist, the aim is not only to identify those in need of urgent excision due to invasive cancer, but also to identify high-risk lesions, with considerable potential to progress to invasive disease, such as those with severe dysplasia or in situ disease, for example, lentigo maligna. Given differences in setting, prior testing, observer qualifications, experience and training, the anticipated performance in terms of accuracy is likely to vary.

When diagnosing potentially life-threatening conditions such as melanoma, the consequences of falsely reassuring a person that they do not have skin cancer can be serious and potentially fatal, as the resulting delay to diagnosis means that the window for successful early treatment may be missed. To minimise these false-negative diagnoses, a good diagnostic test will demonstrate high sensitivity and a high negative predictive value (NPV), where very few of those with a negative test result will actually have a melanoma. Giving falsely positive test results (meaning the test has poor specificity and a high false-positive rate) resulting in the removal of lesions that turn out to be benign is arguably less of an error than missing a potentially fatal melanoma, but is not cost free. False-positive diagnoses not only cause unnecessary scarring from the biopsy or excision procedure, but also increase patient anxiety whilst they await the definite histology results and increase healthcare costs as the number needed to remove to yield one melanoma diagnosis increases.

Alternative test(s)

We have reviewed a number of other tests as part of our series of Cochrane diagnostic test accuracy (DTA) reviews on the diagnosis of melanoma. In particular, dermoscopy has become an essential tool for the specialist clinician and is increasingly being taken up in primary care settings. Dermoscopy (also referred to as dermatoscopy or epiluminescence microscopy or ELM) uses a hand-held microscope and incident light (with or without oil immersion) to reveal subsurface images of the skin at increased magnification of x 10 to x 100 (Kittler 2011). Used alongside clinical examination, dermoscopy has been shown in some studies to increase the sensitivity of clinical diagnosis of melanoma from around 60% to as much as 90% (Bono 2006; Carli 2002a; Kittler 1999; Stanganelli 2000) with much smaller effects in others (Benelli 1999; Bono 2002a). The accuracy of dermoscopy depends on the experience of the examiner (Kittler 2011), with ac-

curacy when used by untrained or less experienced examiners potentially no better than clinical inspection alone (Binder 1997; Kittler 2002).

Pattern analysis (Pehamberger 1993; Steiner 1987) is thought to be the most specific and reliable technique to aid dermoscopy interpretation when used by specialists (Maley 2014); however, dermoscopic histological correlations have been established and diagnostic algorithms developed based on colour, aspect, pigmentation pattern, and skin vessels (e.g. the ABCD rule for dermoscopy (Nachbar 1994; Stolz 1994), the Menzies (Menzies 1996) and the seven-point dermoscopy checklist (Annessi 2007; Argenziano 1998; Argenziano 2001; Gereli 2010; amongst others). Dermoscopy used in addition to visual inspection (in-person evaluations) or used alone (dermoscopic image interpretation remotely from the patient concerned) are the subject of a separate systematic review (Dinnes 2018).

Other relevant tests that we have looked at as part of this series of reviews include teledermatology, mobile phone applications, reflectance confocal microscopy, optical coherence tomography, computer-assisted diagnosis or artificial intelligence-based techniques, and high-frequency ultrasound (Dinnes 2015a). Evidence permitting, we will compare the accuracy of available tests in an overview review, exploiting within-study comparisons of tests and allowing the analysis and comparison of commonly used diagnostic strategies where tests may be used singly or in combination.

We also considered and excluded a number of tests from review, including tests used in the context of monitoring people, such as total body photography of those with large numbers of typical or atypical naevi, and finally, histopathological confirmation following lesion excision. The latter is the established reference standard for melanoma diagnosis and will be one of the standards against which we evaluate the index tests in these reviews.

Rationale

Our series of reviews of diagnostic tests used to assist clinical diagnosis in either clinical practice or in a research setting aims to identify the most accurate approaches to diagnosis and to provide clinical and policy decision-makers with the highest possible standard of evidence on which to base diagnostic and treatment decisions. With increasing rates of melanoma and a trend to adopt the use of dermoscopy and other high-resolution image analysis in primary care, the anxiety around missing early cases needs to be balanced against the risk of over-referrals, to avoid sending too many people with benign lesions for a specialist opinion. It is questionable whether all skin cancers picked up by sophisticated techniques contribute to morbidity and mortality or whether newer technologies run the risk of increasing false-positive diagnoses. It is also possible that use of some technologies, for example, widespread use of dermoscopy in primary care with no training, could actually result in harm by missing melanomas if they are used as replacement technologies for traditional history-taking and clinical examination of the entire skin. Many branches of medicine have noted the danger of such "gizmo idolatry" amongst doctors (Leff 2008). The trend toward remote interpretation of dermatology images (whether clinical or dermoscopic images) and the use of remote technologies that do not involve clinicians without substantive evidence could further disrupt clinical pathways and healthcare payments as they may attract custom from the worried well, leaving an ever decreasing pool of qualified doctors to pick up any resulting problems.

There are few available systematic reviews in the field. The literature searches for the most comprehensive systematic reviews of visual inspection were carried out up to 2007 (Vestergaard 2008) or are focused on specific clinical questions, for example, specific healthcare professionals (Corbo 2012 including only direct comparisons of the accuracy of primary care physicians versus dermatologists, and Loescher 2011 reviewing the skin cancer detection skills of advanced practice nurses) or settings (Herschorn 2012 including direct comparisons of visual inspection versus dermoscopy in primary care). More recently, Harrington and colleagues (Harrington 2017) published a systematic review of clinical prediction rules (or published algorithms) used to assist the diagnosis of melanoma; however, the requirement for a clinical prediction rule does not allow comparison of accuracy with and without the use of an algorithm.

The critical question about the accuracy of visual inspection alone and the impact of examiner, prior patient testing, underlying risk status, and the use of images for diagnosis needs to be answered before the potential contribution of additional diagnostic tests can be set in context and appropriately placed in the diagnostic pathway.

This review follows a generic protocol that covers the full series of Cochrane DTA reviews for the diagnosis of melanoma (Dinnes 2015a). The Background and Methods sections of this review therefore use some text that was originally published in the protocol (Dinnes 2015a) and text that overlaps some of our other reviews (Dinnes 2018).

OBJECTIVES

To determine the diagnostic accuracy of visual inspection for the detection of cutaneous invasive melanoma and atypical intraepidermal melanocytic variants in adults.

Accuracy was estimated separately according to the prior testing undergone by study participants:

- those with limited prior testing, that is, primary presentation; and
- those referred for further evaluation of a suspicious lesion, that is, referred participants.

Accuracy was also estimated separately according to whether the diagnosis was recorded based on a face-to-face (in-person) encounter or based on remote (image-based) assessment.

Secondary objectives

For the identification of cutaneous invasive melanoma and atypical intraepidermal melanocytic variants:

- to determine the diagnostic accuracy of individual algorithms used to assist visual inspection; and
- to determine the effect of observer experience on diagnostic accuracy.

For the alternative definitions of the target condition:

- to determine the diagnostic accuracy of visual inspection for the detection of invasive melanoma alone in adults;
- to determine the diagnostic accuracy of visual inspection for the detection of any skin cancer or skin lesion with a high risk of progression to melanoma in adults (i.e. requiring excision).

Investigation of sources of heterogeneity

We set out to address a range of potential sources of heterogeneity for investigation across our series of reviews, as outlined in our generic protocol (Dinnes 2015a) and described in Appendix 5; however, our ability to investigate these was necessarily limited by the available data on each individual test reviewed.

The sources of heterogeneity that we investigated for visual inspection were:

- in-person versus image-based evaluations;
- study setting: primary, community or private care versus secondary versus specialist clinics;
- use of a diagnostic algorithm: no algorithm reported versus any named algorithm used;
- type of reference standard: histology alone versus histology plus clinical follow-up or other reference standard; and
- disease prevalence: $\leq$ 10% versus > 10%. We chose the 10% cut-off based on advice from clinical co-authors (RB, HW).

METHODS

Criteria for considering studies for this review

Types of studies

We included test accuracy studies that allow comparison of the result of the index test with that of a reference standard, including the following:

- studies where all participants receive a single index test and a reference standard;
- studies where all participants receive more than one index test(s) and reference standard;
- studies where participants are allocated (by any method) to receive different index tests or combinations of index tests and all receive a reference standard (between-person comparative studies (BPC));
- studies that recruit series of participants unselected by true disease status (referred to as case series for the purposes of this review);
- diagnostic case-control studies that separately recruit diseased and non-diseased groups (see Rutjes 2005); however, we did not include studies that compared results for malignant lesions to those for healthy skin (i.e. with no lesion present);
- both prospective and retrospective studies; and
- studies where previously acquired clinical or dermoscopic images were retrieved and prospectively interpreted for study purposes.

We excluded studies from which we could not extract 2x2 contingency data or if they included fewer than five melanoma cases or fewer than five benign lesions. The size threshold of five is arbitrary. However, such small studies are unlikely to add precision to the estimate of accuracy.

Studies available only as conference abstracts were excluded; however, attempts were made to identify full papers for potentially relevant conference abstracts (Searching other resources).

Participants

We included studies in adults with pigmented skin lesions or lesions suspicious for melanoma or those at high risk of developing melanoma, including those with a family history or previous history of melanoma skin cancer, atypical or dysplastic naevus syndrome, or genetic cancer syndromes.

We excluded studies that recruited only participants with malignant or benign diagnoses.

We excluded studies conducted in children or that clearly reported inclusion of more than 50% of participants aged 16 and under.

Index tests

Studies reporting accuracy data for visual inspection alone, with either image-based or in-person diagnosis, were eligible for inclusion. For in-person visual inspection, diagnosis is undertaken in a clinic setting with the patient present (face-to-face diagnosis). For these studies we assumed that patient history-taking would have taken place and is likely to have contributed to lesion diagnosis; however, we did not specifically extract details of patient history-taking due to anticipated poor reporting in the primary studies. For image-based studies, diagnosis is based on clinical or 'macro' images (photographs), remotely from the study participant. For

these studies, we extracted any additional patient information that was provided to assist diagnosis.

We included all established algorithms or checklists to assist diagnosis by visual inspection. We included studies developing new algorithms or methods of diagnosis (i.e. derivation studies) if they:

- used a separate independent 'test set' of participants or images to evaluate the new approach; or
- investigated lesion characteristics that had previously been suggested as associated with melanoma and the study reported accuracy based on the presence or absence of particular combinations of characteristics.

We excluded studies if they:

- used a statistical model to produce a data-driven equation, or algorithm based on multiple diagnostic features, with no separate test set;
- used cross-validation approaches such as 'leave-one-out' cross-validation (Efron 1983);
- evaluated the accuracy of the presence or absence of individual lesion characteristics or morphological features, with no overall diagnosis of malignancy;
- reported accuracy data for 'clinical diagnosis' with no clear description as to whether the reported data related to visual inspection alone;
- were based on the experience of a particular skin cancer clinic, where dermoscopy may or may not have been used on an individual patient-basis.

Although primary care clinicians can in practice be specialists in skin cancer, we considered primary care physicians as generalist practitioners and dermatologists as specialists. Within each group, we extracted any reporting of special interest or accreditation in skin cancer.

Target conditions

We defined the primary target condition as the detection of:

- any form of invasive cutaneous melanoma or atypical intraepidermal melanocytic variants (i.e. including melanoma in situ, or lentigo maligna, which has a risk of progression to invasive melanoma).

We considered two additional definitions of the target condition in secondary analyses, namely the detection of:

- any form of invasive cutaneous melanoma alone;
- any skin lesion requiring excision. This latter definition includes melanoma plus other forms of skin cancer, such as BCC and cSCC, as well as melanoma in situ, lentigo maligna, and lesions with severe melanocytic dysplasia.

The diagnosis of the keratinocyte skin cancers, BCC, and SCC as primary target conditions are the subject of a separate series of reviews (Dinnes 2015b).

Reference standards

The ideal reference standard is histopathological diagnosis in all eligible lesions. A qualified pathologist or dermatopathologist should perform histopathology. Ideally, reporting should be standardised detailing a minimum dataset to include the histopathological features of melanoma to determine the American Joint Committee on Cancer (AJCC) Staging System (e.g. Slater 2014). We did not apply reporting of a minimum dataset as a necessary inclusion criterion, but extracted any pertinent information.

Partial verification (applying the reference test only to a subset of those undergoing the index test) was of concern given that lesion excision or biopsy are unlikely to be carried out for all benign-appearing lesions within a representative population sample. Therefore, to reflect what happens in reality, we accepted clinical follow-up of benign-appearing lesions as an eligible reference standard, whilst recognising the risk of differential verification bias (as misclassification rates of histopathology and follow-up will differ).

Additional eligible reference standards included cancer registry follow-up and 'expert opinion' with no histology or clinical follow-up. Cancer registry follow-up is considered less desirable than active clinical follow-up, as follow-up is not carried out within the control of the study investigators. Furthermore, if participant-based analyses as opposed to lesion-based analyses are presented, it may be difficult to determine whether the detection of a malignant lesion during follow-up is the same lesion that originally tested negative on the index test.

All of the above were considered eligible reference standards with the following caveats:

- all study participants with a final diagnosis of the target disorder must have a histological diagnosis, either subsequent to the application of the index test or after a period of clinical follow-up; and
- at least 50% of all participants with benign lesions must have either a histological diagnosis or clinical follow-up to confirm benignity.

Search methods for identification of studies

Electronic searches

The Information Specialist (SB) carried out a comprehensive search for published and unpublished studies. A single large literature search was conducted to cover all topics in the programme grant (see Appendix 1 for a summary of reviews included in the programme grant). This allowed for the screening of search results for potentially relevant papers for all reviews at the same time. A search combining disease related terms with terms related to the test names, using both text words and subject headings was formulated. The search strategy was designed to capture studies evaluating tests for the diagnosis or staging of skin cancer. As the

majority of records were related to the searches for tests for staging of disease, a filter using terms related to cancer staging and to accuracy indices was applied to the staging test search, to try to eliminate irrelevant studies, for example, those using imaging tests to assess treatment effectiveness. A sample of 300 records that would be missed by applying this filter was screened and the filter adjusted to include potentially relevant studies. When piloted on MEDLINE, inclusion of the filter for the staging tests reduced the overall numbers by around 6000. The final search strategy, incorporating the filter, was subsequently applied to all bibliographic databases as listed below (Appendix 6). The final search result was cross-checked against the list of studies included in five systematic reviews; our search identified all but one of the studies, and this study was not indexed on MEDLINE. The Information Specialist devised the search strategy, with input from the Information Specialist from Cochrane Skin. No additional limits were used.
We searched the following bibliographic databases to 29 August 2016 for relevant published studies:

- MEDLINE via OVID (from 1946);
- MEDLINE In-Process & Other Non-Indexed Citations via OVID; and
- Embase via OVID (from 1980).

We searched the following bibliographic databases to 30 August 2016 for relevant published studies:

- the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 7) in the Cochrane Library;
- the Cochrane Database of Systematic Reviews (CDSR; 2016, Issue 8) in the Cochrane Library;
- Cochrane Database of Abstracts of Reviews of Effects (DARE; 2015, Issue 2);
- CRD HTA (Health Technology Assessment) database, 2016, Issue 3; and
- CINAHL (Cumulative Index to Nursing and Allied Health Literature via EBSCO from 1960).

We searched the following databases for relevant unpublished studies using a strategy based on the MEDLINE search:

- CPCI (Conference Proceedings Citation Index), via Web of Science™ (from 1990; searched 28 August 2016); and
- SCI Science Citation Index Expanded™ via Web of Science™ (from 1900, using the 'Proceedings and Meetings Abstracts' Limit function; searched 29 August 2016).

We searched the following trials registers using the search terms 'melanoma', 'squamous cell', 'basal cell' and 'skin cancer' combined with 'diagnosis':

- Zetoc (from 1993; searched 28 August 2016).
- The US National Institutes of Health Ongoing Trials Register (www.clinicaltrials.gov); searched 29 August 2016.
- NIHR Clinical Research Network Portfolio Database (www.nihr.ac.uk/research-and-impact/nihr-clinical-research-network-portfolio/); searched 29 August 2016.
- The World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/); searched 29 August 2016.

We aimed to identify all relevant studies regardless of language or publication status (published, unpublished, in press, or in progress) and applied no date limits.

Searching other resources

We have included information about potentially relevant ongoing studies in the Characteristics of ongoing studies tables. We have screened relevant systematic reviews identified by the searches for their included primary studies, and included any missed by our searches. We have checked the reference lists of all included papers, and subject experts within the author team reviewed the final list of included studies. We did not conduct any citation searching.

Data collection and analysis

Selection of studies

At least one review author (JDi or NC) screened titles and abstracts, with any queries discussed and resolved by consensus. A pilot screen of 539 MEDLINE references showed good agreement (89% with a kappa of 0.77) between screeners. We included at initial screening primary test accuracy studies and test accuracy reviews (for scanning of reference lists) of any test used to investigate suspected melanoma, BCC, or cSCC. Both a clinical reviewer (from one of a team of twelve clinician reviewers) and a methodologist reviewer (JDi or NC) independently applied Inclusion criteria (Appendix 7) to all full text articles, disagreements were resolved by consensus or by a third party (JDe, CD, HW, and RM). We contacted authors of eligible studies when insufficient data were presented to allow for the construction of 2x2 contingency tables.

Data extraction and management

One clinical (as detailed above) and one methodologist reviewer (JDi, NC or LFR) independently extracted data concerning details of the study design, participants, index test(s) or test combinations and criteria for index test positivity, reference standards, and data required to populate a 2x2 diagnostic contingency table for each index test using a piloted data extraction form. We extracted data at all available index test thresholds. We resolved disagreements by consensus or by consulting a third party (JDe, CD, HW, and RM).
We contacted authors of included studies where information related to final lesion diagnoses or diagnostic thresholds were missing. In particular, invasive cSCC (included as disease-positive for

one of our secondary objectives) is not always differentiated from 'in situ' variants such as Bowen's disease (which we did not consider as disease-positive for any of our definitions of the target condition). We contacted authors of conference abstracts published from 2013 to 2015 to ask whether full data were available. If no full paper was identified, we marked conference abstracts as 'pending' and will revisit them in a future review update.

Dealing with multiple publications and companion papers

Where we identified multiple reports of a primary study, we maximised yield of information by collating all available data. Where there were inconsistencies in reporting or overlapping study populations, we contacted study authors for clarification in the first instance. If this contact with authors was unsuccessful, we used the most complete and up-to-date data source where possible.

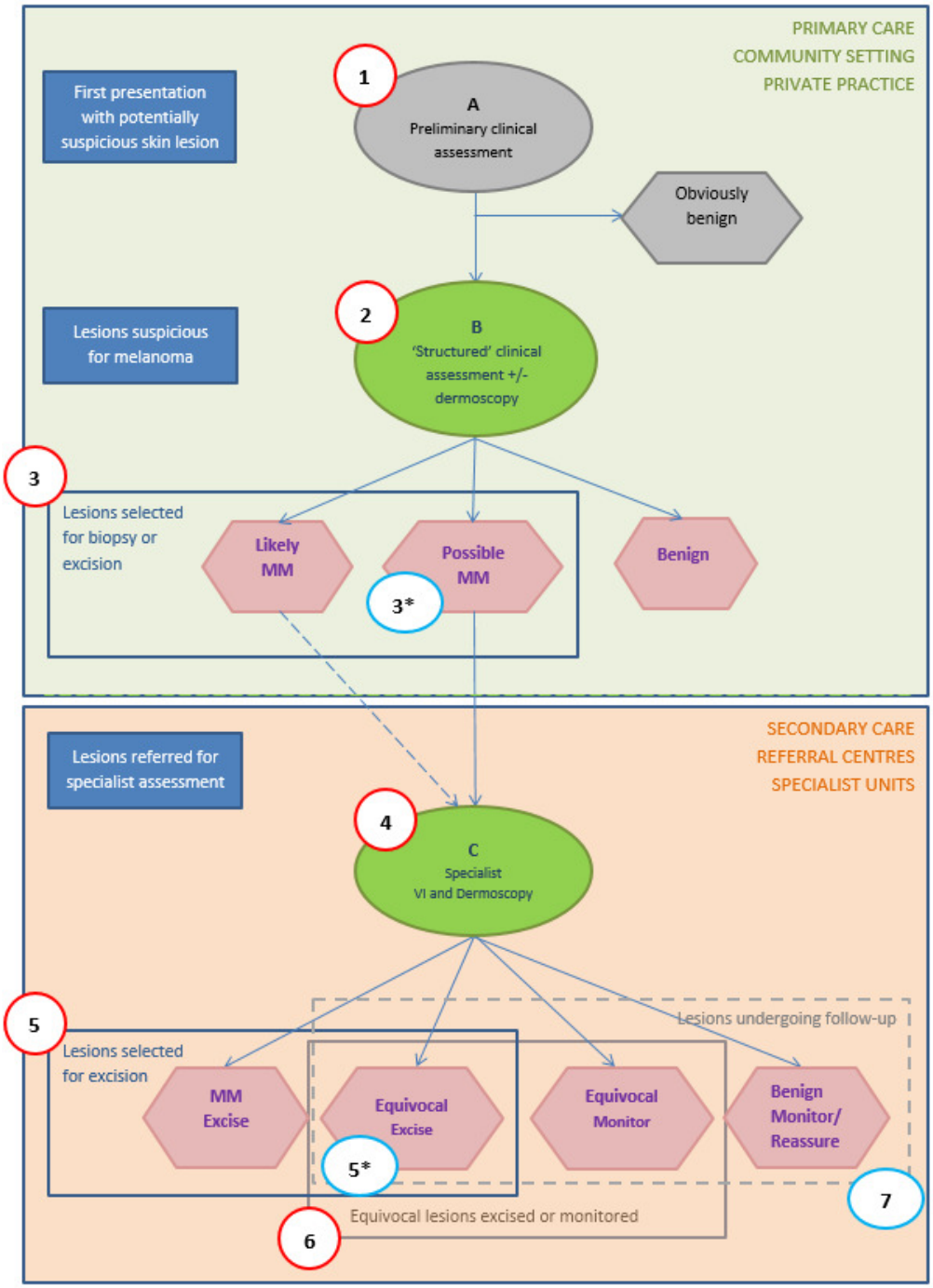
Assessment of methodological quality

We assessed risk of bias and applicability of included studies using the QUADAS-2 checklist (Whiting 2011), tailored to the review topic (see Appendix 8) and piloted it on a small number of included full-text articles. One clinical (as detailed above) and one methodologist reviewer (JDi, NC or LFR) independently assessed quality for the remaining studies; we resolved any disagreement by consensus or by consulting a third party where necessary (JDe, CD, HW, and RM).

Statistical analysis and data synthesis

We conducted separate analyses according to the point that study participants reached in the clinical pathway (numbered from 1 to 7 in Figure 3), the clarity with which the pathway could be determined (clear or unclear), and the evaluation of in-person versus image-based diagnosis.

Figure 3. Clinical pathway



Our unit of analysis was the lesion rather than the participant. This is because firstly, in skin cancer, initial treatment is directed to the lesion rather than systemically (thus it is important to be able to correctly identify cancerous lesions for each person), and secondly, it is the most common way in which the primary studies reported data. Although there is a theoretical possibility of correlations of test errors when the same people contribute data for multiple lesions, most studies include very few people with multiple lesions and any potential impact on findings is likely to be very small, particularly in comparison with other concerns regarding risk of bias and applicability. Where an individual study assessed multiple algorithms, we selected datasets on the following preferential basis:

- 'no algorithm' reported; data presented for clinician's overall diagnosis or management decision;
- pattern analysis or pattern recognition;
- ABCD algorithm (or derivatives of);
- seven-point checklist (also referred to as Glasgow/MacKie checklist).

Where multiple thresholds per algorithm were reported, we included the standard or most commonly used threshold. If data for multiple observers were reported, we used data for the most experienced observer, using single observer diagnosis in preference to a consensus or average across observers. If we were unable to choose a dataset based on the above 'rules', we made a random selection of one dataset per study. To allow comparisons of tests, we have included data on the accuracy of dermoscopy in a separate review in our series (Dinnes 2018).

For each analysis, we plotted estimates of sensitivity and specificity on coupled forest plots and in receiver operating characteristic (ROC) space. For tests where commonly used thresholds were reported we estimated summary operating points (summary sensitivities and specificities) with 95% confidence intervals and prediction regions using the bivariate hierarchical model (Chu 2006; Reitsma 2005). Where inadequate data were available for the model to converge the model was simplified, first by assuming no correlation between estimates of sensitivity and specificity and secondly by setting estimates of near zero variance terms to zero (Takwoingi 2015). Where all studies reported 100% sensitivity (or 100% specificity) we summed the number with disease (or no disease) across studies and used it to compute a binomial exact 95% confidence interval.

For computation of likely numbers of true-positive, false-positive, false-negative and true-negative findings in the 'Summary of findings' tables, we applied these indicative values to lower quartile, median and upper quartiles of the prevalence observed in the study groups. We have reported these numbers for the average operating point on the SROC curve in 'Summary of findings' tables.

Investigations of heterogeneity

We investigated heterogeneity, and made comparisons between algorithms and according to observer experience by comparing summary ROC curves using the hierarchical summary receiver-operator curves (HSROC) model (Rutter 2001). HSROC curves allow incorporation of data at different thresholds and from different algorithms or checklists. We used an HSROC model that assumed a constant SROC shape between tests and subgroups, but allowed for differences in threshold and accuracy by addition of covariates. We assessed the significance of the differences between tests or subgroups by the likelihood ratio test assessing differences in both accuracy and threshold, and by a Wald test on the parameter estimate testing for differences in accuracy alone. We fitted simpler models when convergence was not achieved due to small numbers of studies, first assuming symmetric SROC curves (setting the shape term to zero), and then setting random-effects variance estimates to zero. We have presented estimates of accuracy from HSROC models as diagnostic odds ratios (DORs) (estimated where the SROC curve crosses the sensitivity=specificity line) with 95% confidence intervals. We have presented differences between tests and subgroups from HSROC analyses as relative diagnostic odds ratios (RDORs) with 95% confidence intervals.

We fitted bivariate models using the xtmelogit command in STATA 15 and HSROC models using the NLMIXED procedure in the SAS statistical software package (SAS 2012; version 9.3; SAS Institute, Cary, NC, USA) and the metadas macro (Takwoingi 2010).

Sensitivity analyses

We planned sensitivity analyses, restricting analyses to studies at the least risk of bias; however, these were not carried out due to insufficient study numbers.

Assessment of reporting bias

Because of uncertainty about the determinants of publication bias for diagnostic accuracy studies and the inadequacy of tests for detecting funnel plot asymmetry (Deeks 2005), we did not perform tests to detect publication bias.

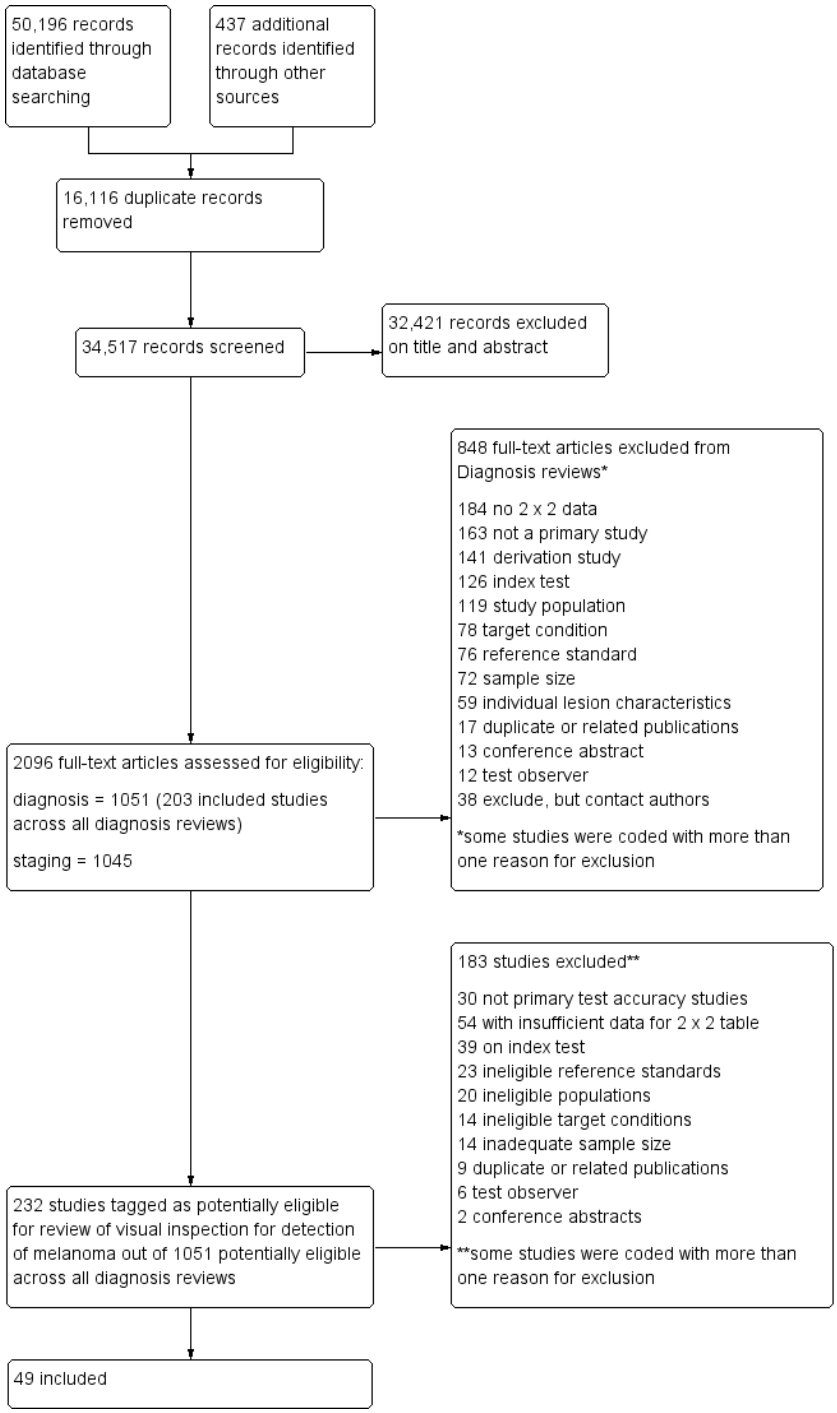
RESULTS

Results of the search

The Information Specialist identified a total of 34,517 unique references and we screened them for inclusion. Of these, we reviewed

1051 full-text papers for eligibility for any one of the suite of reviews of tests to assist in the diagnosis of melanoma or keratinocyte skin cancer. Of the 1051 full-text papers assessed, we excluded 848 from all reviews in our series (see Figure 4; PRISMA flow diagram of search and eligibility results).

Figure 4. PRISMA flow diagram.



Of the 232 studies tagged as potentially eligible for this review of visual inspection, we included 49 publications, reporting 49 individual studies. Exclusions were mainly due to the inability to construct a 2x2 contingency table based on the data presented (n = 54); the use of ineligible index tests (n = 39) (for example: reporting of data for visual inspection and dermoscopy only (n = 12), reporting of data for 'clinical diagnosis' (n = 11), or for serial use of the index test in a follow-up context (n = 7)); or not meeting our requirements for an eligible reference standard (n = 23). Other reasons for exclusion included ineligible study populations (n = 20) (for example, recruiting only malignant or only benign lesions (n = 18)), inadequate sample size (n = 14), ineligible definition of the target condition (n = 14) or with test interpretation by medical students or laypeople (n = 6). A list of the 183 publications excluded from this review with reasons for exclusion is provided in Characteristics of excluded studies, with a list of all studies excluded from the full series of reviews available as a separate pdf (please contact skin.cochrane.org for a copy of the pdf).

We contacted the authors of 14 publications for the purposes of this review of visual inspection and, to date, have received responses about seven publications. One response allowed the inclusion of the study in the review (Walter 2012), five provided clarifications on methods used on studies included (Bono 2006; Bourne 2012; Rosendahl 2011; Stanganelli 2000; Walter 2012); one replied with the information needed but the two studies could not be included due to the evaluation of 'clinical diagnosis' (Youl 2007a; Youl 2007b); and five replied but were not able to provide the information requested in relation to eight study publications, one of which we could still include (Menzies 2009) and seven we could not (Fabbrocini 2008; Freeman 1963; Heal 2008; Menzies 2009; Warshaw 2009a; Warshaw 2009b; Warshaw 2010).

The 49 included study publications report on a total of 51 cohorts of lesions and 134 datasets with 34,351 lesions and 2499 malignancies. The total number of study participants with suspicious lesions cannot be estimated due to lack of reporting in study publications. Two thirds of studies (n = 32; 65%) also reported accuracy data for diagnosis using dermoscopy; these comparisons are reported in Dinnes 2018. Seven studies reported data for additional tests including teledermatology (n = 1) and computer-assisted diagnosis techniques (n = 6).

Methodological quality of included studies

We have summarised the overall methodological quality of all included studies (n = 49) in Figure 5 and Figure 6.

Figure 5. Risk of bias and applicability concerns graph: review authors' judgements about each domain presented as percentages across included studies

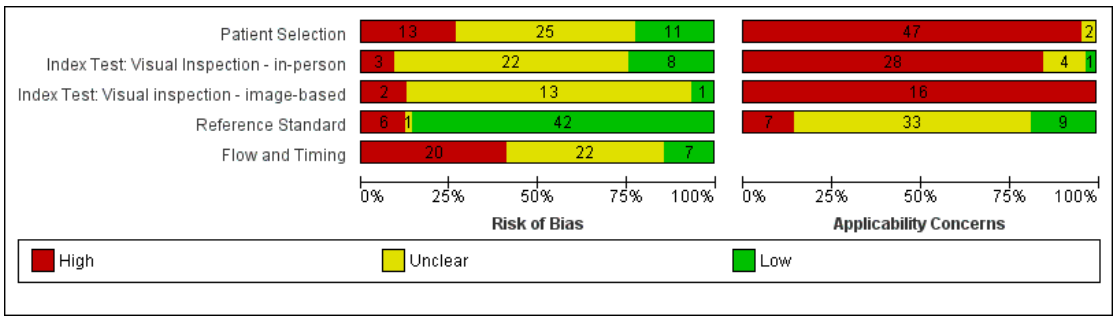
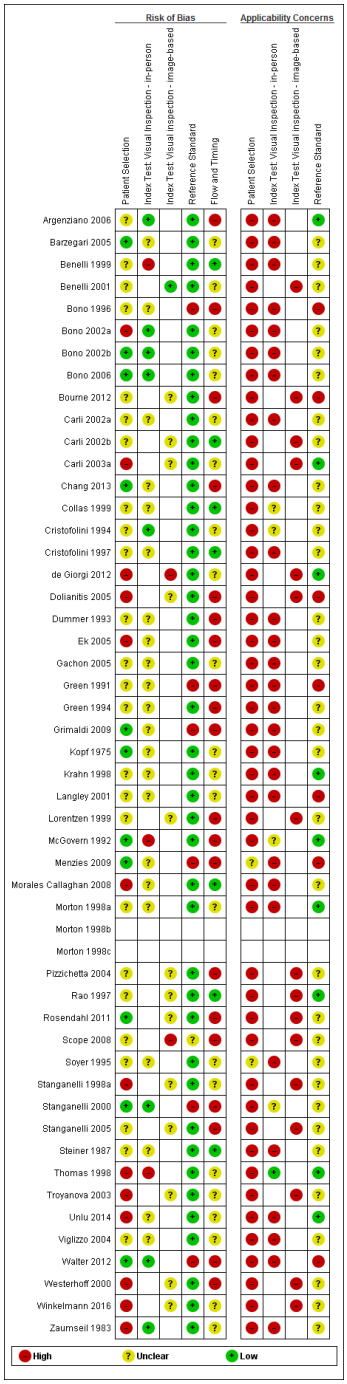


Figure 6. Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study



The majority of study reports provided insufficient information across almost all study quality domains to allow us to judge the risk of bias, while we scored applicability of study findings as of 'High' concern in three of four domains assessed.

Participant selection

We judged only 22% of studies (n = 11) at low risk of bias for participant selection and 27% (n = 13) at high risk of bias. Ten studies (20%) either used a case-control type design with separate selection of melanoma cases and lesions with benign diagnoses (n = 6) or did not clearly describe the study design used (n = 5). Over half (55%; n = 27) reported random or consecutive participant recruitment; the remaining 45% did not describe recruitment methods. Over half of studies (53%) did not describe whether they had applied any exclusion criteria and we judged them at unclear risk of bias. Seven studies (14%) applied inappropriate participant exclusions, excluding 'difficult to diagnose' lesions such as awkwardly located lesions (Bono 2002a; Morales Callaghan 2008; Unlu 2014); those with disagreement on histopathology (de Giorgi 2012; Ek 2005; Zaumseil 1983); or dermoscopically 'peculiar' lesions (Carli 2003a).

We considered almost all cohorts (96%; n = 47) at high concern for applicability of participants. In the majority of cases (n = 41), high concern was due to restricted study populations: inclusion of only melanocytic (n = 10) or amelanotic (n = 1) lesions; restriction by lesion diameter (Bono 2002b; Bono 2006; Steiner 1987); or, most commonly, inclusion of lesions selected for excision based on the clinical or dermoscopic diagnosis or selected retrospectively from histopathology databases (n = 37). We judged only four cohorts to have included a representative patient population (Grimaldi 2009; Menzies 2009; Stanganelli 2000; Walter 2012). Fourteen cohorts also included multiple lesions per participant, with only eight clearly including a similar number of participants and lesions (Bono 2002a; Bono 2002b; Bono 2006; Bourne 2012; Collas 1999; Krahn 1998; Pizzichetta 2004; Unlu 2014).

Index test

For the index test domain, we considered studies separately according to whether they reported in-person evaluations of visual inspection (n = 33) or evaluations based on interpretation of clinical images (image-based evaluations; n = 16). For the in-person evaluations, we judged 24% (n = 8) at low risk of bias, and 9% (n = 3) at high risk; 22 (67%) did not provide sufficient information to allow us to judge the risk of bias fully. We considered that all studies made the diagnosis blinded to the reference standard result: 24% (n = 8) also clearly reported pre-specification of the diagnostic threshold (five of the eight using named algorithms (Argenziano 2006; Cristofolini 1994; Stanganelli 2000; Walter 2012; Zaumseil 1983 and three by the same author team (Bono 2002a; Bono 2002b; Bono 2006) describing the process by which they had reached the diagnosis. Three studies developed new algorithms (Thomas 1998) or evaluated multiple thresholds for test positivity (Benelli 2001; McGovern 1992). Reporting was poorer for the image-based evaluations, with over three quarters of studies (n = 13) not providing sufficient information to allow us to judge the risk of bias fully, one study (6%) judged at low risk of bias and two (12%) at high risk. Again, we considered that all the studies had made the diagnosis blinded to the reference standard result, with one prospectively testing two pre-specified diagnostic thresholds (Benelli 2001) and two (de Giorgi 2012; Scope 2008) testing multiple diagnostic thresholds.

We recorded high concern for the applicability of the index tests for 85% (n = 28) of in-person evaluations. High concern was primarily due to a lack of description of the diagnostic thresholds used (n = 24), but also as a result of presentation of average (Argenziano 2006) or consensus diagnoses (Barzegari 2005; Benelli 1999; Carli 2002a; Cristofolini 1997; Morales Callaghan 2008; Steiner 1987) as opposed to the diagnosis of a single observer. Two studies were also judged to have reported diagnosis by non-expert observers (Menzies 2009; Walter 2012), both of which reported diagnoses by large groups of primary care practitioners. In reality, specific expertise in diagnosing pigmented lesions does vary amongst examiners, for example Menzies 2009 requiring a history of excision or referral of at least 10 pigmented skin lesions over the previous 12-month period but excluding those already using dermoscopy or digital monitoring of lesions, and Walter 2012 excluding those with specialist dermatology training but reporting some training in dermatology for almost a quarter of participating GPs. We judged almost three quarters of studies (n = 24) to have applied and interpreted the 'test' in a clinically applicable manner, nine (27%) provided sufficient detail of the threshold used and 11 (33%) described the observers as expert or experienced. All image-based studies were of high concern for applicability, due to the image-based nature of interpretation limiting the clinical applicability of findings but also the lack of detail on the thresholds used (n = 13). A higher proportion (62%; n = 10) described the observers as expert or experienced.

Reference standard

Of the 49 included cohorts, we judged 85% at low risk of bias for the reference standard due to the use of an acceptable reference standard (n = 42). Six did not meet our criteria for an acceptable reference standard, with more than 20% of the benign lesions having only expert diagnosis with no clinical follow-up (Bono 1996; Green 1991; Grimaldi 2009; Menzies 2009; Stanganelli 2000; Walter 2012), three of which were primary care-based studies (Grimaldi 2009; Menzies 2009; Walter 2012). We recorded

blinding of the reference standard to the index test (in this case the pathology referral diagnosis) but it did not contribute to the overall risk of bias for the reference standard domain. Three studies implemented no blinding of the reference standard (Menzies 2009 and Walter 2012 referring patients for excision under standard practice and Thomas 1998 describing a form recording the presence or absence of each ABCDE criterion to the usual pathology form) and the remaining 46 studies did not describe blinding (94%). The applicability of the reference standard was of low concern in nine studies (18%), high in seven (14%), and unclear for 33 (67%). In all cases, high concern was due to the use of expert opinion for classifying the final diagnosis of some lesions. The majority of studies (n = 40; 82%) did not report histopathology interpretation by an experienced histopathologist or by a dermatopathologist.

Participant flow

In terms of flow and timing, we judged 20 cohorts at high risk of bias, seven at low risk, and 22 did not provide enough information on which to judge this domain. Of those at high risk, 11 cohorts did not use the same reference standard for all participants (differential verification), and 15 did not include all participants in the analysis either due to incomplete information (Argenziano 2006; Bono 1996; Ek 2005; McGovern 1992; Menzies 2009; Pizzichetta 2004; Walter 2012); inadequate images (Chang 2013; Dolianitis 2005; Green 1994; Lorentzen 1999; Pizzichetta 2004; Rosendahl 2011; Scope 2008); and exclusion of particular lesion groups following recruitment (Bourne 2012; Dummer 1993; Menzies 2009). A further 37 cohorts were unclear on the interval between the application of the index test and excision for histology with 12 reporting consecutive diagnosis and excision or biopsy.

Findings

1. Target condition: invasive melanoma and atypical intraepidermal melanocytic variants

Thirty-seven studies reported accuracy data for the detection of invasive melanoma and atypical intraepidermal melanocytic variants, one of which reported data for three different sets of lesions (Morton 1998a; Morton 1998b; Morton 1998c), giving a total of 39 datasets; the studies conducted 28 evaluations in person and 11 were image-based.

We have summarised details of the in-person studies in Appendix 9, with quality assessments in Appendix 10. Summary details of the image-based studies are in Appendix 11 with quality assessments in Appendix 12. Details of established algorithms used to assist diagnosis are described in detail in Appendix 4. Results for the primary analyses are presented in Table 1. We have presented forest plots of study data for each analysis in Table 1 in Figure 7 and Figure 8; summary estimates are depicted in Figure 9 and Figure 10. Table 2 reports heterogeneity investigations, Table 3 compares test algorithms and Table 4 compares observers.

Figure 7. Forest plot of in-person evaluations of visual inspection for detection of invasive melanoma and atypical intraepidermal melanocytic variants by point on the clinical pathway where they are diagnosed

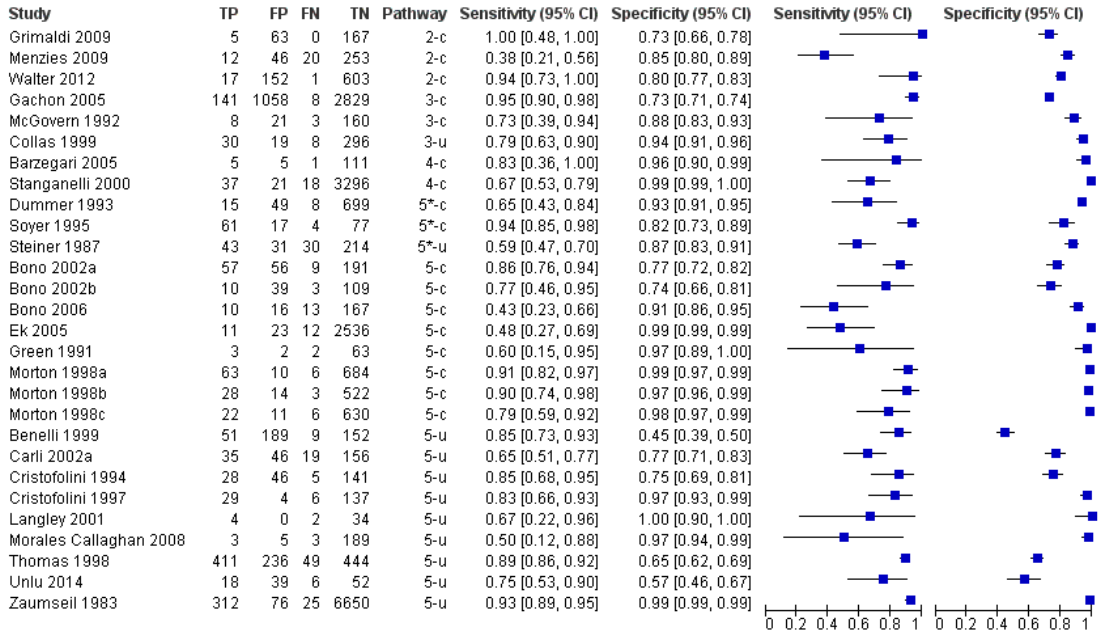


Figure 8. Forest plot of image-based evaluations of visual inspection for detection of invasive melanoma and melanocytic intraepidermal variants by point on the clinical pathway where they are diagnosed

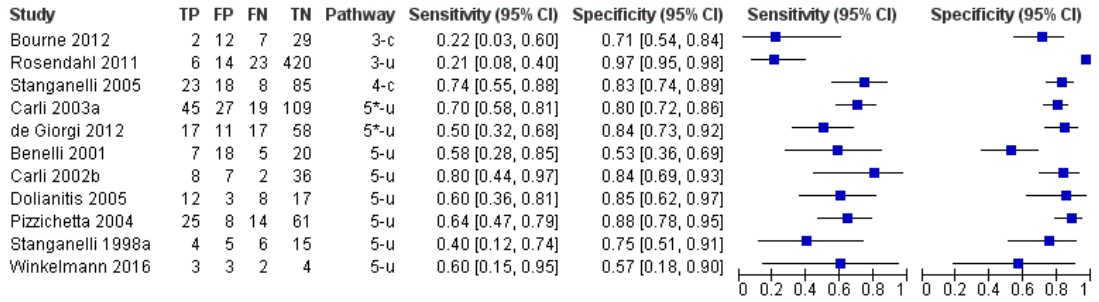


Figure 9. Summary estimates of accuracy of in-person visual inspection for the detection of invasive melanoma and melanocytic intraepidermal variants by point on the clinical pathway where they are diagnosed (confidence regions are not plotted due to small numbers of studies)

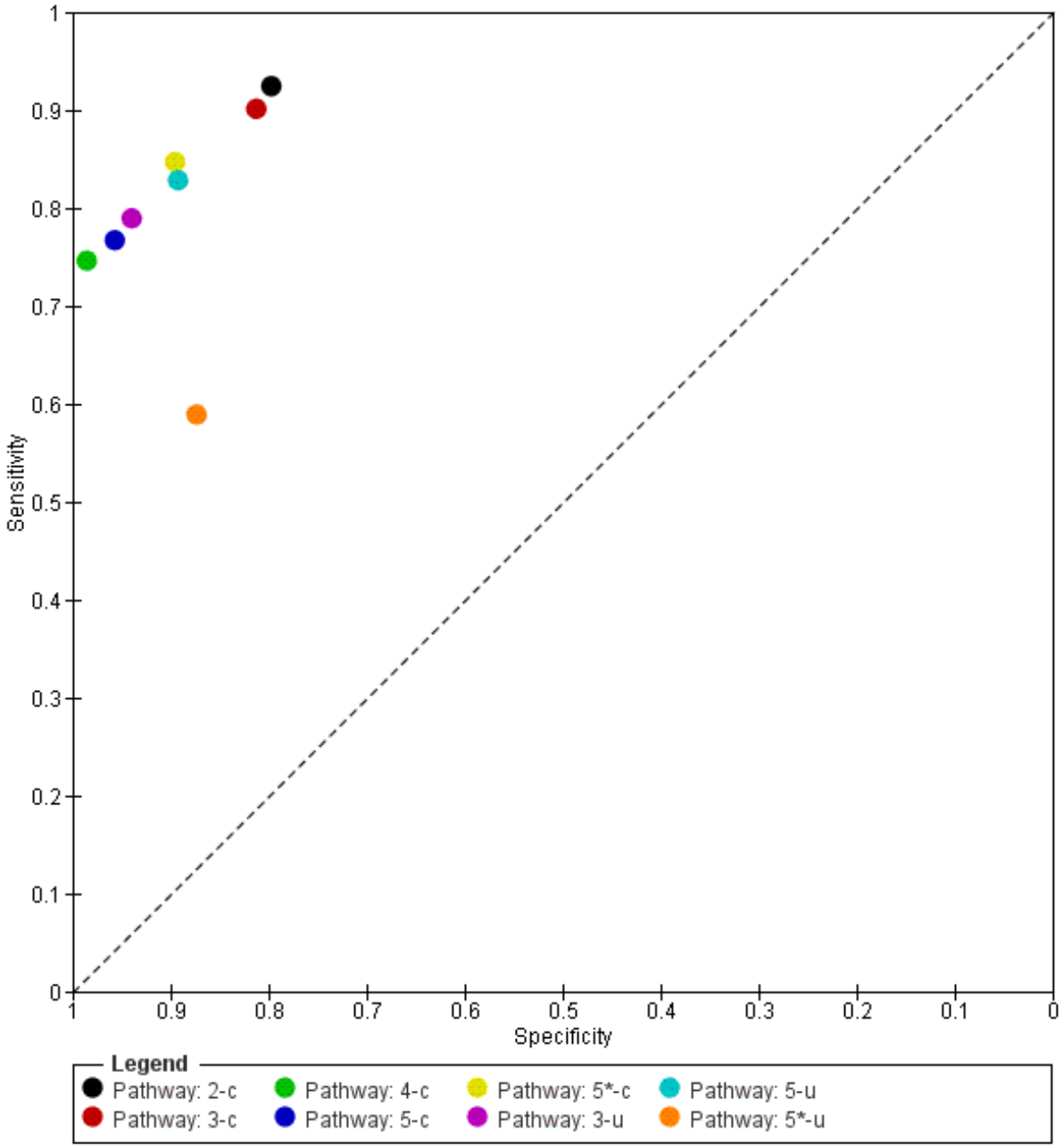
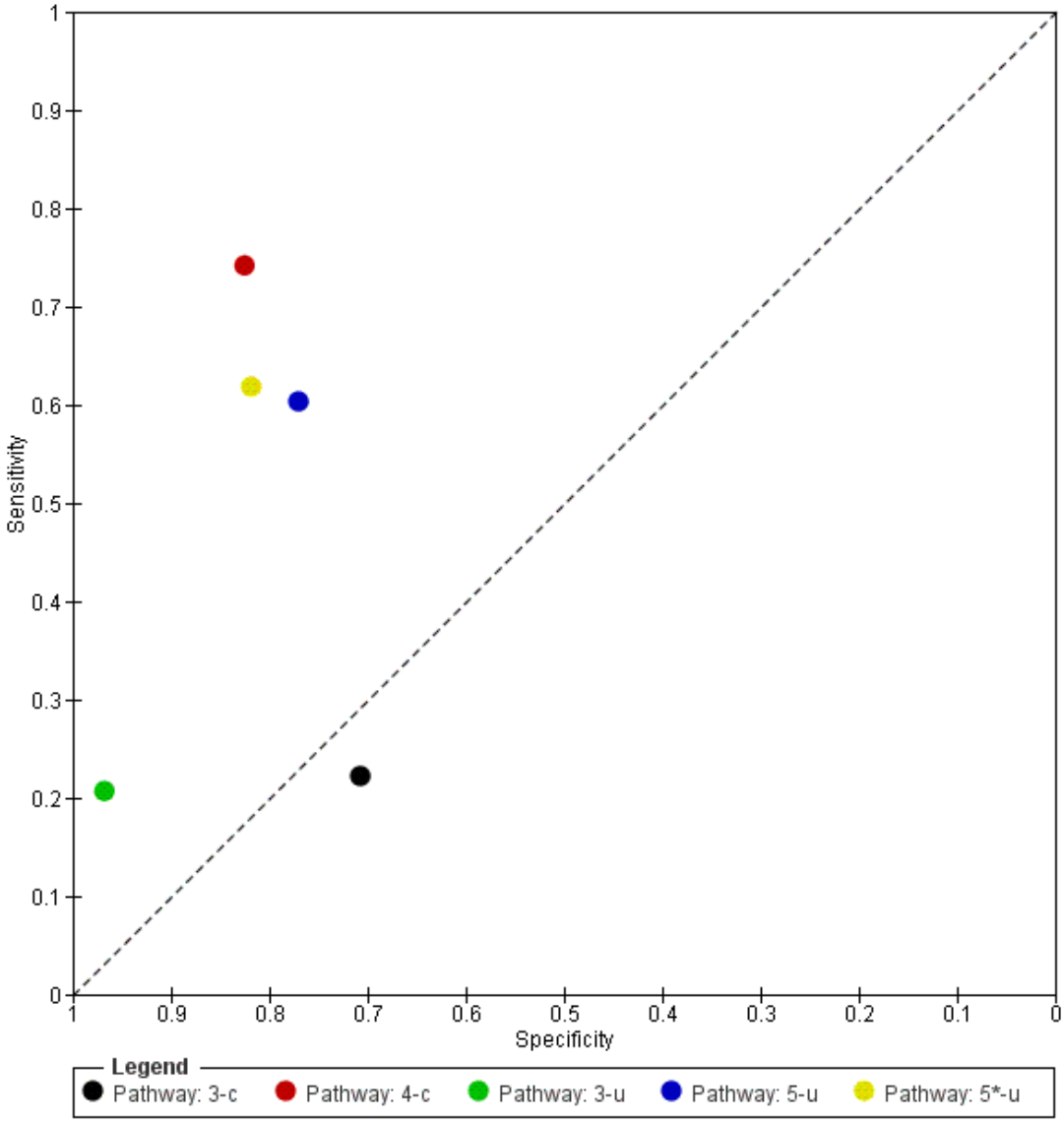


Figure 10. Summary estimates of accuracy of image-based visual inspection for the detection of invasive melanoma and melanocytic intraepidermal variants by point on the clinical pathway where they are diagnosed (confidence regions are not plotted due to small numbers of studies)



In-person evaluations

Of the 28 evaluations conducted on an in-person basis, 17 contained enough information to describe where on the clinical pathway they had assessed participants (coded as 'clear' on pathway),

and we considered 11 not to have provided sufficient information to allow us to identify the pathway (coded 'unclear' on pathway). We considered these evaluations according to position on the pathway and clear versus unclear pathway classification (Table 1). Figure 7 presents the results of the individual studies grouped by their position on the pathway; Figure 9 depicts the summary estimates at each point on the pathway.

Studies in participants with limited prior testing

Six in-person evaluations of visual inspection recruited series of participants with pigmented lesions, who were presenting for a first structured clinical assessment of a suspicious lesion (Collas 1999; Gachon 2005; Grimaldi 2009; McGovern 1992; Menzies 2009; Walter 2012) (Appendix 9; Appendix 10). All studies included participants with pigmented lesions; Gachon 2005 restricted inclusion to melanocytic lesions only. The prevalence of disease ranged from 4% to 6% in four studies, with Collas 1999 (11%) and Grimaldi 2009 (20%) reporting higher prevalence of melanoma. Three studies prospectively included all participants presenting in primary care within a given time frame and were clearly positioned on the clinical pathway (Pathway 2-c in Figure 9):

- summary sensitivity was 92.4% (95% CI 26.2% to 99.8%) and specificity 79.7% (95% CI 73.7% to 84.7%) (1339 lesions and 55 melanomas; Grimaldi 2009; Menzies 2009; Walter 2012).

The studies supplemented histological diagnosis with clinical follow-up of at least three months for lesions considered benign (all three studies) and two included expert clinical diagnosis without follow-up for some benign lesions (Menzies 2009; Walter 2012). Three studies included only participants with lesions selected for excision (Pathway 3-c and 3-u in Figure 9): two were conducted in private dermatology clinics (Collas 1999; Gachon 2005) and one at an open access veterans' dermatology clinic (McGovern 1992) (Appendix 9):

- summary sensitivity was 90.1% (95% CI 70.0% to 97.3%) and specificity 81.3% (95% CI 67.5% to 90.0%) for two studies clearly positioned on the clinical pathway (Pathway 3-c; 4228 lesions and 160 melanomas; Gachon 2005; McGovern 1992);
- sensitivity was 78.9% (95% CI 62.75% to 90.4%) and specificity 94.0% (95% CI 90.7% to 96.3%) (353 lesions and 38 melanomas; Collas 1999) in the single study that could not be clearly positioned on the clinical pathway (Pathway 3-u).

Diagnosis was recorded by primary care physicians with a range of experience (Grimaldi 2009; Menzies 2009; Walter 2012) or by dermatologists (Collas 1999; Gachon 2005; McGovern 1992) with no obvious differences in sensitivity or specificity. Four studies reported no formal algorithm to assist diagnosis. Two of these classified lesions 'suspicious for malignancy' as test-positive (Gachon 2005; Grimaldi 2009) and two reported data for 'correct' or 'primary' diagnosis of melanoma (Collas 1999; Menzies 2009). Walter 2012 reported data for MacKie's revised seven-point checklist (MacKie 1990) at a threshold of ≥ 3, and McGovern 1992 used the BCD algorithm at ≥ 2 characteristics present (this study also reported data using the original seven-point checklist, see 'Analyses by algorithm' reported below).

Studies in referred participants

Studies conducted 22 in-person evaluations of visual inspection in participants referred for specialist assessment. We were able to position 12 clearly on the clinical pathway (three evaluations from a single study) and 10 did not provide sufficient information for us to make a clear assessment (Figure 7; Appendix 9; Appendix 10).

We judged two studies to include all participants referred for further assessment (Pathway 4-c in Figure 9) and both were clearly positioned on the clinical pathway:

- summary sensitivity was 74.6% (95% CI 48.9% to 90.0%) and specificity 98.6% (95% CI 94.7% to 99.6%) (3494 lesions and 61 melanomas; Barzegari 2005; Stanganelli 2000).

Fifteen studies providing 17 datasets included only those with any lesion selected for excision (Pathway 5-c and 5-u in Figure 9):

- summary sensitivity was 76.7% (95% CI 61.7% to 87.1%) and specificity 95.7% (95% CI 89.7% to 98.3%) (5331 lesions and 258 melanomas) for six studies (with eight datasets) clearly positioned on the clinical pathway (Pathway 5-c; Bono 2002a; Bono 2002b; Bono 2006; Ek 2005; Green 1991; Morton 1998a; Morton 1998b; Morton 1998c);
- summary sensitivity was 82.8% (95% CI 74.4% to 88.9%) and specificity 89.2% (95% CI 71.1% to 96.5%) (9611 lesions and 1015 melanomas) for nine studies that could not be clearly positioned on the clinical pathway (Pathway 5-u; Benelli 1999; Carli 2002a; Cristofolini 1994; Cristofolini 1997; Langley 2001; Morales Callaghan 2008; Thomas 1998; Unlu 2014; Zaumseil 1983).

We considered three studies to report data only for those participants with equivocal or difficult-to-diagnose lesions selected for excision (Pathway 5*-c and 5*-u in Figure 7 and Figure 9):

- summary sensitivity was 84.7% (95% CI 55.5% to 96.1%) and specificity 89.5% (95% CI 79.5% to 95.0%) (930 lesions and 88 melanomas) for two studies clearly positioned on the clinical pathway (Pathway 5*-c; Dummer 1993; Soyer 1995);
- sensitivity was 61.4% (95% CI 49.0% to 72.9%) and specificity 87.3% (95% CI 82.5% to 91.2%) (318 lesions and 73 melanomas) in one study not clearly positioned on the clinical pathway (Pathway 5*-u; Steiner 1987).

Studies included pigmented lesions referred for further evaluation at a dermatology or pigmented lesion clinic, two restricting to melanocytic lesions only (Morales Callaghan 2008; Unlu 2014) and four restricting by lesion diameter (≤ 3 mm (Bono 2006), ≤ 6 mm (Bono 2002b), < 10 mm (Steiner 1987), or ≤ 15 mm

(Barzegari 2005)). The prevalence of disease ranged from 1% (Ek 2005) to 41% (Soyer 1995). Disease prevalence was generally lower in studies clearly positioned on the clinical pathway (11% or less in 7 of 10 datasets) compared to those that could not be clearly positioned (7 of 9 datasets reporting disease prevalence of 15% or over (Appendix 9)). The prevalence of melanoma in studies of equivocal lesions was 3% (Dummer 1993), 23% (Steiner 1987) and 41% (Soyer 1995).

Diagnoses were recorded by dermatologists or dermatology residents (or were assumed to be by dermatologists based on study authors' institutions or study settings), by surgical oncologists or by plastic surgeons (Appendix 9). Observer experience was poorly reported, with only seven studies referring to 'experienced' or 'expert' observers; three studies were clearly positioned on the pathway and four not clearly positioned. All studies reported observer diagnosis with no formal algorithm, apart from five using ABCD or ABCDE algorithms (Benelli 1999; Cristofolini 1994; Cristofolini 1997; Thomas 1998; Stanganelli 2000). Diagnosis was more often based on the opinion of a single observer as opposed to a consensus or average decision in studies clearly positioned on the pathway (10 of 12 datasets; Stanganelli 2000; Bono 2002a; Bono 2002b; Bono 2006; Green 1991; Morton 1998a; Morton 1998b; Morton 1998c; Dummer 1993; Soyer 1995) compared to those not clearly positioned (3 of 10 datasets; Thomas 1998; Unlu 2014; Zaumseil 1983).

Image-based evaluations

Of the 11 image-based evaluations, two contained enough information to describe where on the clinical pathway they had assessed participants (coded as 'clear' on pathway), and we considered nine to have provided insufficient information to allow us to identify the pathway (coded 'unclear' on pathway) (Appendix 11 Appendix 12). We have presented the results in Table 1. Figure 8 presents the results of the individual studies grouped by their position on the pathway; Figure 10 depicts the summary estimates at each point on the pathway.

Studies in participants with limited prior testing

Two studies retrospectively reviewed clinical images from participants with lesions excised in primary care settings (Pathway 3-c and 3-u in Figure 10):

- sensitivity was 22.2% (95% CI 2.8% to 60.0%) and specificity 70.7% (95% CI 54.4% to 83.9%) (50 lesions and 9 melanomas) in one study clearly positioned on the clinical pathway (Pathway 3-c; Bourne 2012);
- sensitivity was 20.7% (95% CI 8.0% to 39.7%) and specificity 96.8% (95% CI 94.6% to 98.2%) (463 lesions and 29 melanomas) in the study not clearly positioned on the clinical pathway (Pathway 3-u) (Rosendahl 2011). The study report was unclear as to whether the excisions were undertaken at the primary care practice or in a referral setting.

The prevalence of melanoma was 6% (Rosendahl 2011) and 20% (Bourne 2012) and both studies included a range of different types of lesions. Three GPs and a clinical nurse, with varying levels of dermoscopy experience, reviewed the lesion images in Bourne 2012 and an expert dermatologist reviewed the images in Rosendahl 2011. They made their diagnoses without the aid of a published algorithm.

Studies in referred participants

Nine evaluations of clinical images were conducted in participants referred for specialist assessment; we could clearly position one on the clinical pathway and eight did not provide sufficient information for us to make a clear assessment.

We considered the one study clearly positioned on the clinical pathway to have included all participants referred for further assessment (Pathway 4-c in Figure 10):

- sensitivity was 74.2% (95% CI 55.4% to 88.1%) and specificity 82.5% (95% CI 73.8% to 89.3%) (134 lesions and 31 melanomas; Stanganelli 2005).

Although the remaining eight studies did not provide sufficient information to allow us to clearly position them on the clinical pathway, we assumed that they had obtained lesion images from referral settings (Pathway 5-u and 5*-u in Figure 10):

- summary sensitivity was 60.3% (95% CI 49.2% to 70.5%) and specificity 77.0% (95% CI 63.9% to 86.4%) (293 lesions and 96 melanomas) for six studies that included all lesions selected for excision (Pathway 5-u) (Benelli 2001; Carli 2002b; Dolianitis 2005; Pizzichetta 2004; Stanganelli 1998a; Winkelmann 2016);
- summary sensitivity was 61.9% (95% CI 46.7% to 75.0%) and specificity 81.8% (95% CI 75.2% to 87.0%) (303 lesions and 98 melanomas) across two studies that included participants with equivocal lesions selected for excision (Pathway 5*-u) (Carli 2003a; de Giorgi 2012).

Studies were retrospective case series apart from two case-control type studies (Dolianitis 2005; Winkelmann 2016) and one with an unclear design (Benelli 2001). Three studies (Benelli 2001; Dolianitis 2005; Stanganelli 1998a) evaluated observer accuracy before and after dermoscopy training. All the studies reviewed images of pigmented or melanocytic lesions apart from one that focused on hypomelanotic ($\leq$ 30% pigmentation) or amelanotic lesions (Pizzichetta 2004). The prevalence of melanoma ranged from 19% (Carli 2002b) to 50% (Dolianitis 2005); four studies included only melanomas (including in situ) and benign naevi (Carli 2003a; de Giorgi 2012; Stanganelli 2005; Winkelmann 2016).

Dermatologists or observers with mixed qualifications undertook lesion diagnosis; observer experience was poorly reported (Appendix 11). Stanganelli 2005 also provided accuracy data for the average of three GPs (data reported in section 1.3.2). Most

studies presented average accuracy across observers; only two reported accuracy for a single observer (Benelli 2001; Pizzichetta 2004). All studies except Benelli 2001 (ABCDE algorithm) and de Giorgi 2012 (ABCD) made diagnoses without the use of diagnostic algorithms.

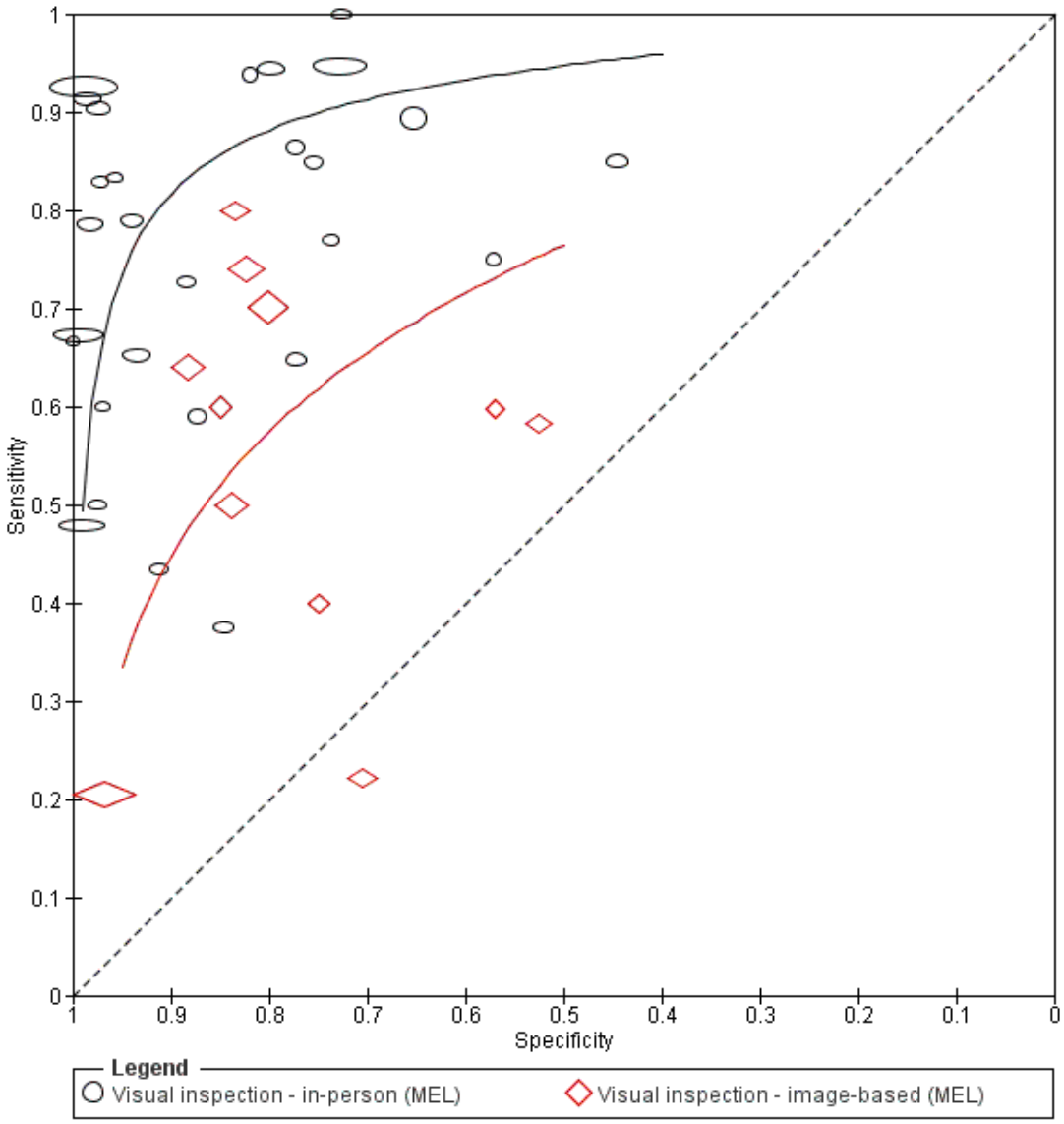
Secondary analyses

We conducted secondary analyses for the detection of invasive melanoma and atypical intraepidermal melanocytic variants, regardless of classification by clinical pathway.

Covariate investigations

A preliminary analysis across the 39 datasets contributing to the primary analyses described above found a large difference in accuracy for in-person evaluations compared to those based on the assessment of clinical images (RDOR 8.54, 95% CI 2.89 to 25.3, P < 0.001; Table 2; Figure 11). The magnitude and importance of the observed difference is so large, raising serious concerns about the applicability of visual inspection studies done via image observation only, that we elected to undertake all subsequent covariate investigations based on in-person evaluations only (n = 28).

Figure 11. Summary ROC comparing in-person and image-based evaluations of visual inspection for detection of invasive melanoma or atypical intraepidermal melanocytic variants (MEL)



For the 28 in-person evaluations, only one of the four covariate investigations approached statistical significance (Table 2); observed accuracy was lower in studies where disease prevalence of melanoma (percentage of cases in the study that tested positive for the reference standard) was over 10% compared to those with disease prevalence of 10% or less (RDOR 0.31, 95% CI 0.09 to 1.00; P = 0.05). The RDOR for study setting (secondary care or specialist clinic compared to primary care) was 1.51 (95% CI 0.32 to 7.09; P = 0.59; Figure 12), for use of a named algorithm to aid diagnosis compared to no algorithm reported was 1.03 (95% CI 0.25 to 4.34; P = 0.96; Figure 13), and for use of histology plus clinical follow-up or other reference standard compared to histology alone was 0.76 (95% CI 0.14 to 4.02; P = 0.74; Figure 14).

Figure 12. Summary ROC plot of in-person visual inspection evaluations stratified by study setting for detection of invasive melanoma and atypical intraepidermal melanocytic variants (MEL)

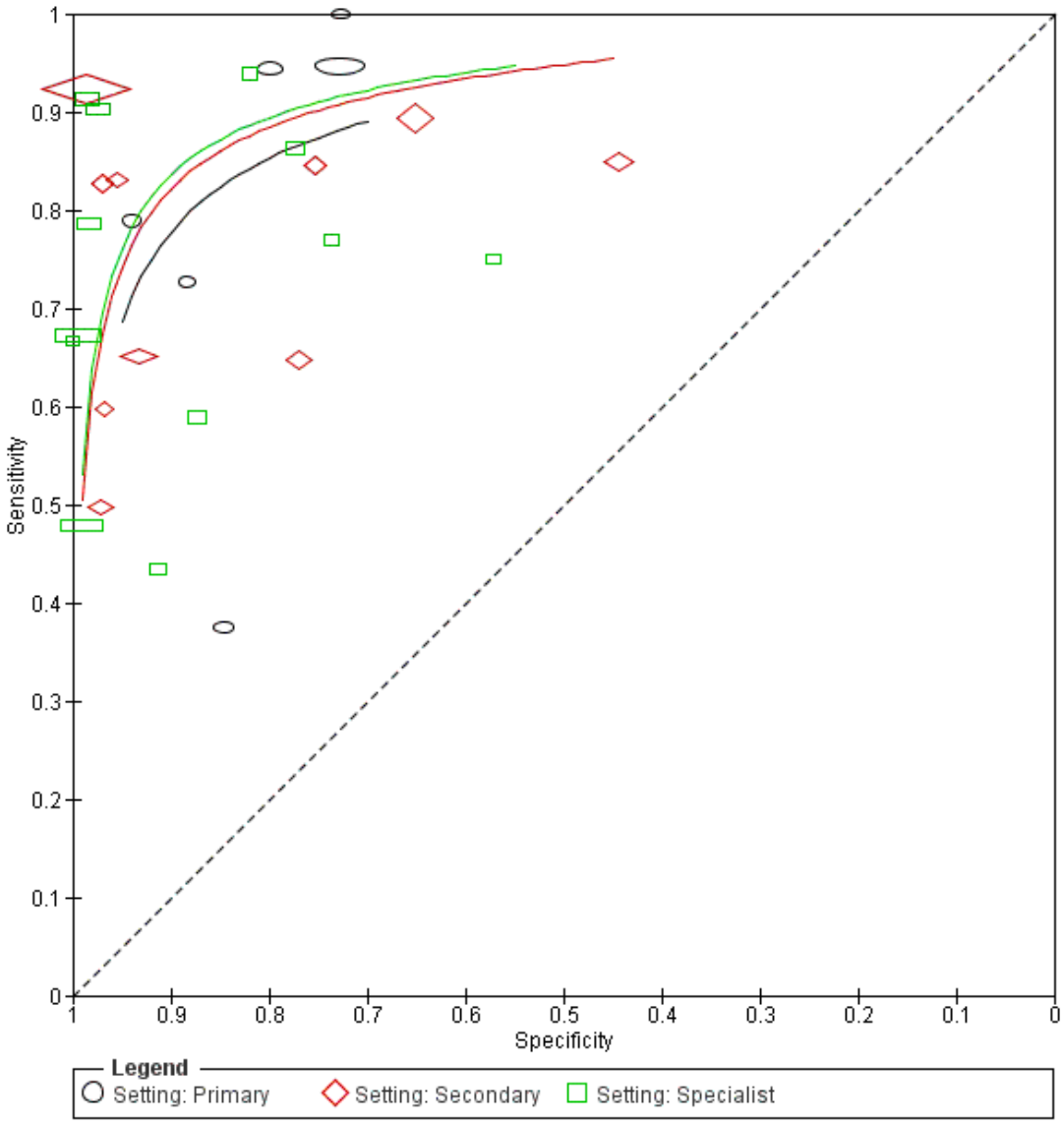


Figure 13. Summary ROC Plot of in-person visual inspection evaluations stratified by use of a published algorithm for detection of invasive melanoma and atypical intraepidermal melanocytic variants (MEL)

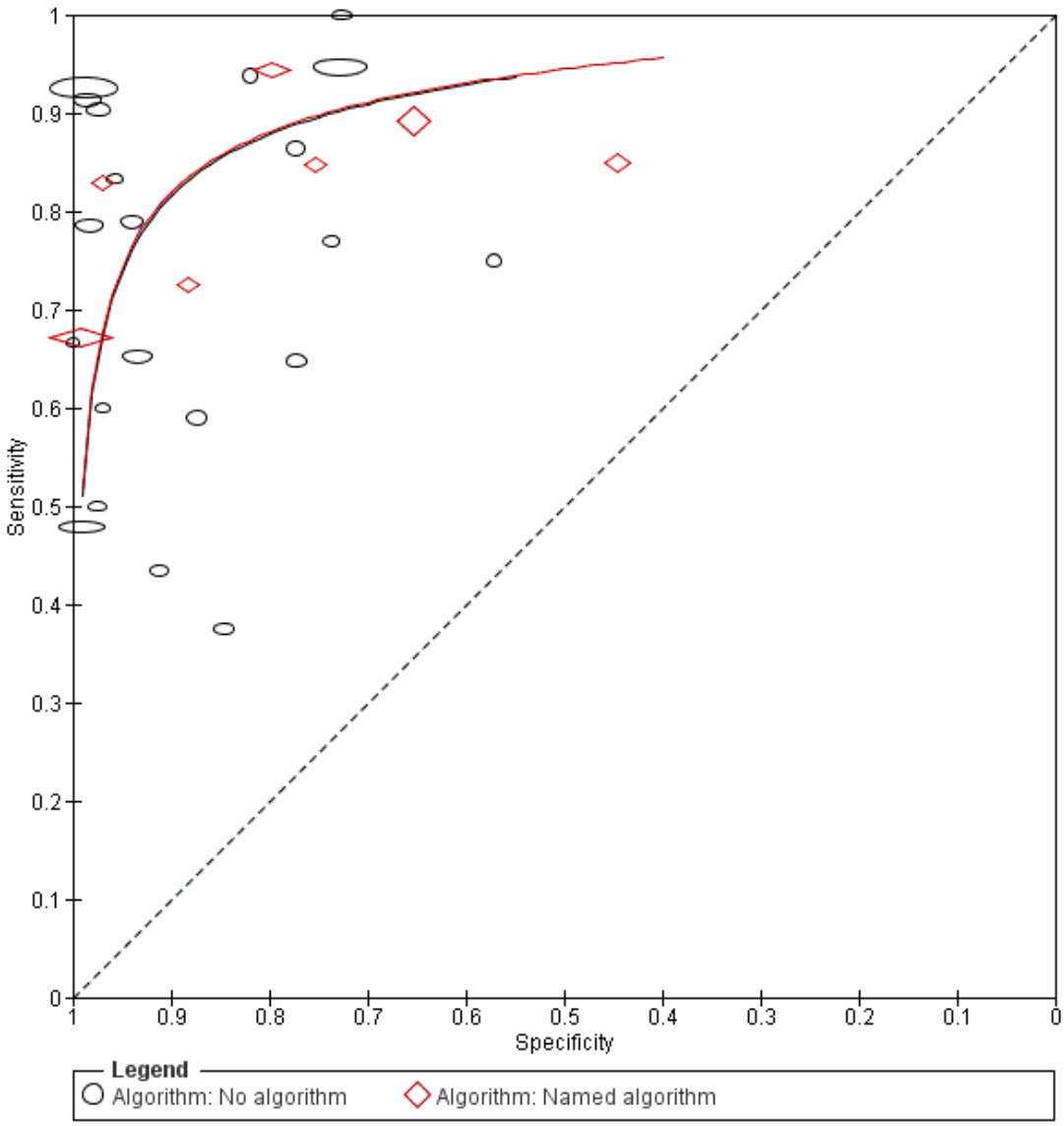
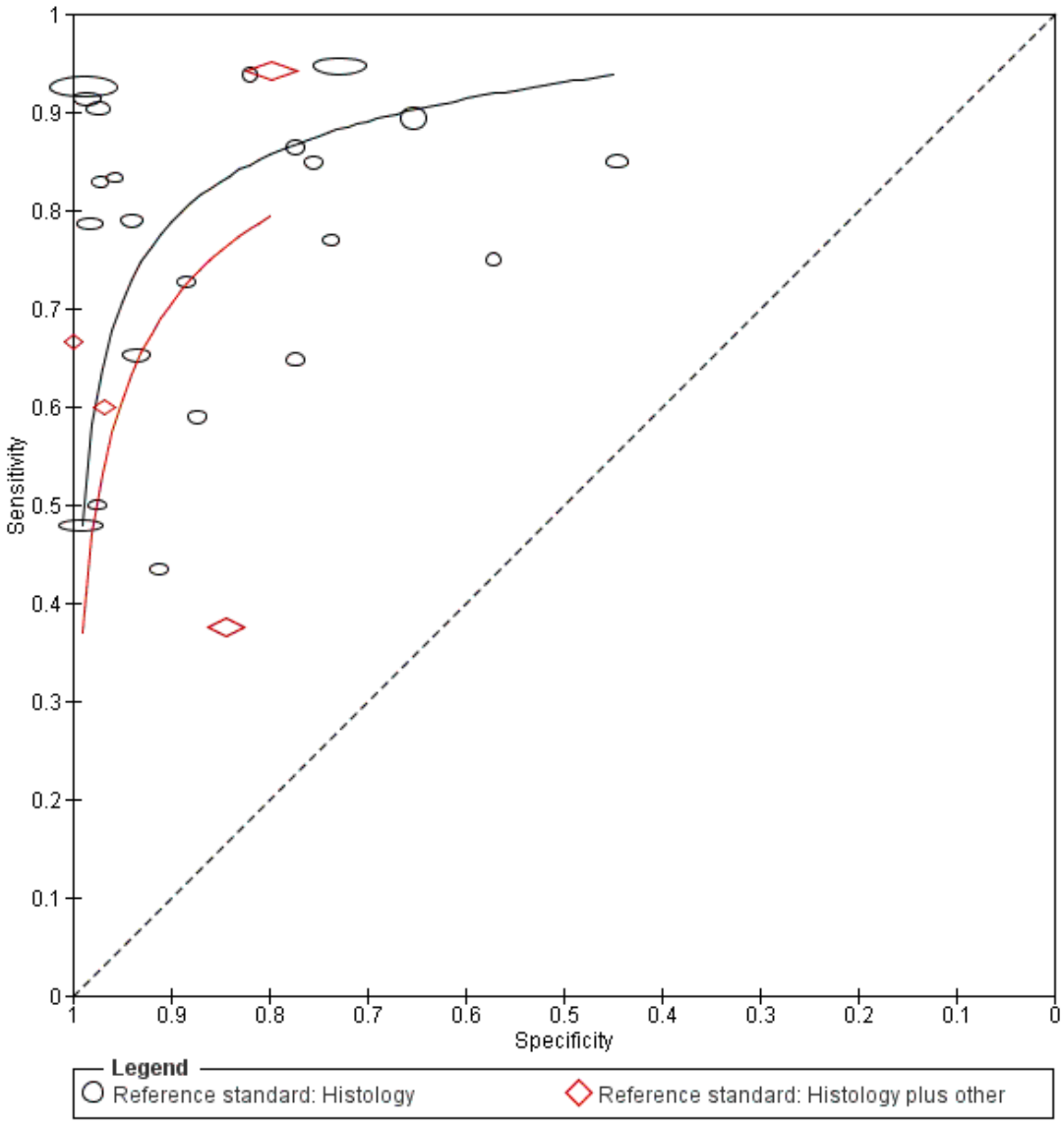


Figure 14. Summary ROC plot of in-person visual inspection evaluations stratified by reference standard for detection of invasive melanoma and atypical intraepidermal melanocytic variants (MEL)



Analyses by algorithms used to assist visual inspection

Of the 28 in-person evaluations only seven reported using an algorithm to assist visual inspection, limiting our ability to make meaningful comparisons between algorithms (Table 3). Observer diagnosis without the use of a formal algorithm (n = 21 datasets) had the highest diagnostic accuracy (DOR 46.2, 95% CI 21.9 to 97.5), with an average sensitivity of 78% (95% CI 68% to 85%) and average specificity of 93% (95% CI 88% to 96%). Pooled sensitivity was slightly higher and specificity slightly lower for variations on the (A)BCD(E) algorithm (n = 6 datasets), but with overlapping confidence intervals (summary sensitivity 83% (95% CI 75% to 88%); summary specificity 88% (95% CI 64% to 97%)). Two datasets reported data for either the original seven-point checklist at a number of thresholds (McGovern 1992) or for the revised seven-point checklist (Walter 2012). At the standard threshold of 3 or above for both algorithms, the highest observed sensitivity and specificity was 94% (95% CI 73% to 100%) and 80% (95% CI 77% to 83%) for the revised version (Walter 2012). The image-based evaluations reported data for either no algorithm or for variations of ABCD(E); we observed a similar pattern with much lower levels of overall accuracy (Table 3).

Analyses by observer experience

Analyses by observer expertise were restricted by the limited amount of information provided in the study reports (Table 4; Appendix 9; Appendix 11). Our analyses are therefore based primarily on study subgroups by observer qualifications (consultant/registrar/mixed qualifications/primary care practitioners), with the 'consultant' category separated into 'Expert consultant' (for any study describing observers as expert or experienced) and 'Consultant' where experience or expertise was not otherwise reported (for example, for those that described observers as dermatologists) (Table 4).

No clear pattern according to observer experience could be discerned for in-person evaluations. RDORs in comparison to the 'Expert consultant' group (9 studies) ranged from 0.45 (95% CI 0.05 to 3.67; P = 0.44) for observers at resident/registrar level (2 studies) to 7.28 (95% CI 0.69 to 76.3; P = 0.09) for GPs (3 studies).

For image-based evaluations, accuracy was highest for the 'Expert consultant' group (DOR 20.5, 95% CI 4.82 to 86.9); RDORs in comparison to the 'expert' group ranged from 0.18 (95% CI 0.04 to 0.90; P = 0.04) for observers described as 'dermatologists' (4 studies) to 0.56 (95% CI 0.04 to 7.51; P = 0.63) for mixed secondary and primary care observers (1 study).

Across all definitions of the target condition, seven studies provided comparative data according to observer qualifications or experience (Table 5). Most were image-based assessments, using no prescribed algorithm to aid diagnosis and reporting average results across groups of observers. We observed some evidence of increased sensitivity and smaller increases in specificity with increasing experience; however, wide variations in accuracy remained, with sensitivity ranging from 58% to 91% for expert dermatologists and specificities from 53% to 99%.

2. Target condition: invasive melanoma only

In this section, we present the results for studies of visual inspection for the identification of invasive melanoma, according to the approach taken for diagnosis: in-person or image-based evaluations. We have presented summary characteristics of studies in Appendix 13 and results of meta-analyses in Table 6. Table 7 compares results in studies reporting data for invasive melanoma alone and for invasive melanoma plus atypical intraepidermal melanocytic variants.

Seven datasets evaluated the accuracy of in-person visual inspection for the detection of invasive melanoma (Bono 1996; Green 1994; Kopf 1975; Krahn 1998; McGovern 1992; Viglizzo 2004; Walter 2012), only two of which also reported data for the primary target condition (McGovern 1992; Walter 2012). All studies were based in secondary care or specialist units apart from Walter 2012 (primary care) and McGovern 1992 (army medical centre dermatology clinic). Studies used a modified version of the ABCD checklist (McGovern 1992), the revised seven-point-checklist (Walter 2012), or no algorithm (n = 5; 71%) to assist diagnosis. The prevalence of melanoma ranged from 2% (Kopf 1975; Walter 2012) to 49% (Krahn 1998). Two studies supplemented a histological reference standard with clinical follow-up (Walter 2012) and expert diagnosis of some benign lesions (Bono 1996; Walter 2012).

Sensitivities ranged from 67% to 100% and specificities ranged from 76% to 100%. In meta-analysis the DOR was 62.4 (95% CI 17.6 to 222) (6857 lesions and 208 melanoma cases). Sensitivity and specificity at the average operating point on the SROC curve were 86% (95% CI 68% to 94%) and 91% (95% CI 81% to 96%) respectively. For the two in-person evaluations that also reported data for the primary target condition (Table 7), specificity estimates were hardly affected due to small numbers of included melanoma in situ lesions (five in McGovern 1992 and two in Walter 2012). Sensitivity however, was higher for detection of invasive melanoma alone in McGovern 1992 (100% versus 73% for detection of invasive melanoma or atypical intraepidermal melanocytic variants) due to correct diagnosis of only two of five in situ melanomas, and was marginally lower in Walter 2012 (93.8% versus 94.4% for detection of invasive melanoma or atypical intraepidermal melanocytic variants) due to correct identification of both in situ melanomas with one invasive melanoma missed.

Five datasets reported the accuracy of image-based visual inspection for the detection of invasive melanoma (Lorentzen 1999; Rao 1997; Scope 2008; Troyanova 2003; Westerhoff 2000), but none of them reported data for the primary target condition. Only two studies used images from normal practice settings (Lorentzen 1999; Rao 1997); one obtained images from a teledermatology company (Scope 2008) and two selected images of melanoma cases and controls for use in dermoscopy training studies (Troyanova 2003; Westerhoff 2000). The prevalence of melanoma ranged from 3% (Scope 2008) to 50% (Troyanova 2003; Westerhoff 2000). Studies used the ABCD checklist (Rao 1997), the ugly duckling approach (Scope 2008), or no algorithm (n = 3) to assist diagnosis. Four evaluations clearly presented only the clinical image with no further patient information (80%), and one (Rao 1997) may have presented observers with a concurrent dermoscopic image of the lesion, as blinding between images was not clearly described.

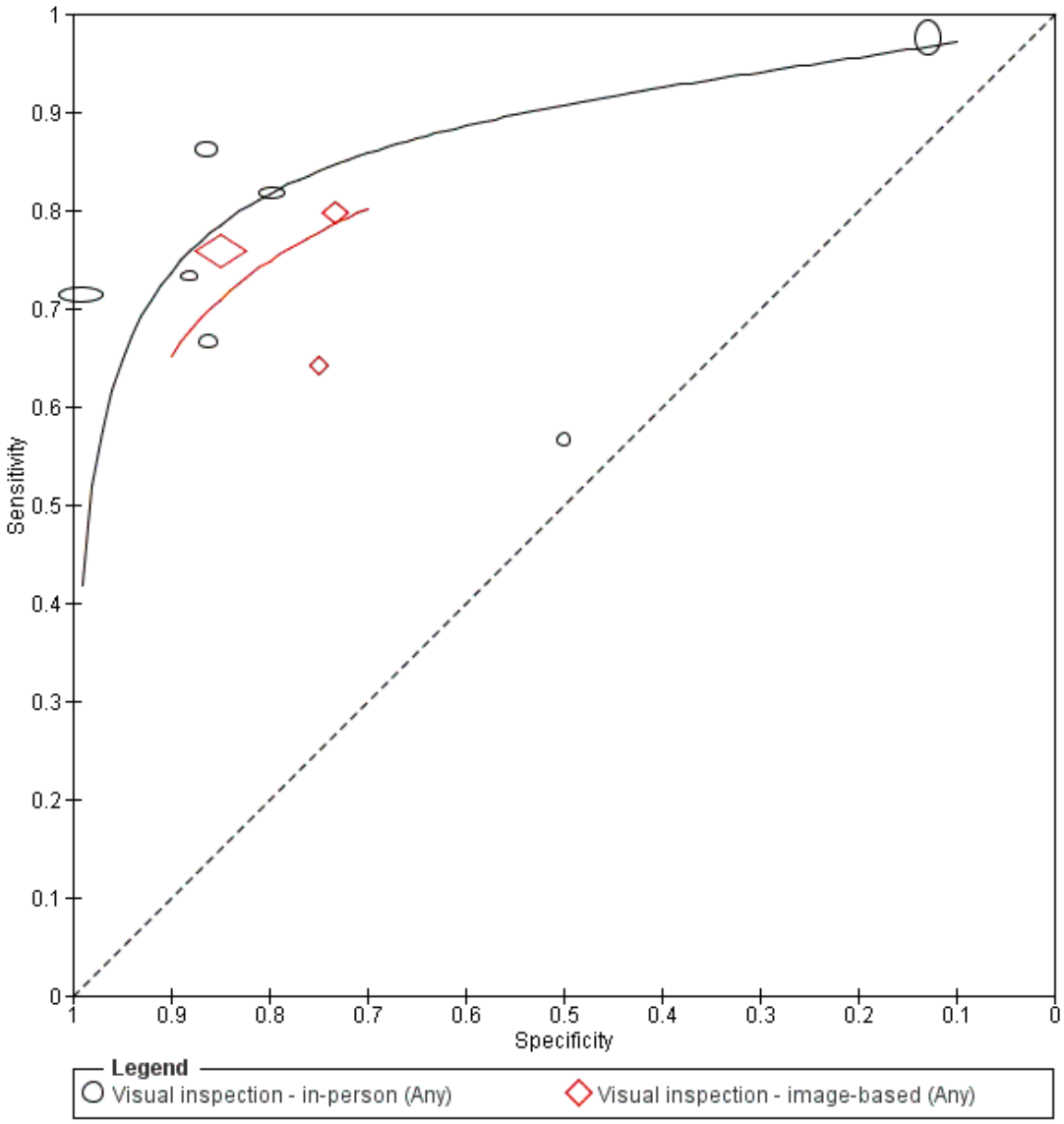
Sensitivities ranged from 62% to 86%; specificities ranged from 54% to 95%. In meta-analysis the DOR was 14.8 (95% CI 3.56 to 61.9) (599 lesions and 150 melanoma cases). Sensitivity and specificity at the average operating point on the SROC curve were 76% (95% CI 50% to 91%) and 83% (95% CI 62% to 93%) respectively.

Accuracy was non-significantly higher for in-person compared to image-based evaluations (RDOR 4.21; 95% CI 0.62 to 28.6; P = 0.13).

3. Target condition: any skin lesion requiring excision

In this section, we present the results for studies of visual inspection for the identification of any skin lesion requiring excision (for each study, we could only extract data for the detection of any skin cancer), according to the approach taken for diagnosis: in-person or image-based evaluations. Summary characteristics of studies are presented in Appendix 14 and results of meta-analyses in Table 6 and Figure 15. Table 7 compares results in studies reporting data for invasive melanoma alone and for invasive melanoma plus atypical intraepidermal melanocytic variants.

Figure 15. Summary ROC comparing in-person and image-based evaluations of visual inspection for detection of any skin lesion requiring excision (any)



Seven datasets evaluated the accuracy of in-person visual inspection for the detection of any skin lesion requiring excision (Argenziano 2006; Chang 2013; Ek 2005; McGovern 1992; Stanganelli 2000; Steiner 1987; Walter 2012). Five of these also reported data for the primary target condition (Ek 2005; McGovern 1992; Stanganelli 2000; Steiner 1987; Walter 2012). Three studies were based in primary care (Argenziano 2006; Walter 2012) or community dermatology clinics (McGovern 1992), the others were based in secondary care or specialist referral clinics. The prevalence of skin cancer ranged from 3% (Walter 2012) to 68% (Ek 2005). Studies used the ABCD algorithm (Argenziano 2006; McGovern 1992; Stanganelli 2000), the revised seven-point-checklist (Walter 2012), or no algorithm (n = 3) to assist diagnosis. Two studies supplemented a histological reference standard with clinical follow-up (Stanganelli 2000; Walter 2012) and expert diagnosis of some benign lesions (Walter 2012).

Sensitivities ranged from 57% to 98%; specificities ranged from 13% to 99%. In meta-analysis the DOR was 20.5 (95% CI 7.11 to 59.3; 8091 lesions and 2187 skin cancer cases). Sensitivity and specificity at the average operating point on the SROC curve were 81% (95% CI 68% to 90%) and 81% (95% CI 56% to 93%) respectively. For the in-person evaluations that also reported data for the primary target condition (Table 7), specificity estimates were not affected in four of the five studies due to the relatively small percentage of other skin cancers in the study populations (BCCs making up 2% of all lesions in McGovern 1992; 1% in Stanganelli 2000 and Walter 2012; and 6% in Steiner 1987). Sensitivities increased in two studies due to a majority of BCCs correctly identified (Stanganelli 2000; Steiner 1987); sensitivity fell in Walter 2012 due to three of four BCCs not being picked up by the revised seven-point checklist; and remained the same in McGovern 1992. We observed a large increase in sensitivity and fall in specificity in Ek 2005, however, as BCCs made up 47% of the total study population and invasive SCCs comprised 20%. When these two lesion groups were considered as disease-positive, sensitivity increased from 48% to 98% and specificity fell from 99% to 13% due to the largely correct identification of BCC and SCC as malignant and high false-positives in the remaining group of lesions considered disease-negative (including large proportions with Bowen's disease, solar keratoses, or seborrhoeic keratoses).

Three datasets reported the accuracy of image-based visual inspection for the detection of any skin lesion requiring excision (Carli 2002b; Rosendahl 2011; Stanganelli 1998a), all of which also reported data for the primary condition. All studies selected images from normal practice settings, two in secondary care (Carli 2002b; Stanganelli 1998a) and one from a primary care practice (Rosendahl 2011). The prevalence of lesions suitable for excision ranged from 22% (Rosendahl 2011) to 47% (Stanganelli 1998a); the latter selecting images for use in a dermoscopy training study. Rosendahl 2011 presented data for a single dermatologist, Carli 2002b for a consensus of two dermatologists, and Stanganelli 1998a presented the average across 20 dermatologists. None of these studies used an algorithm to assist diagnosis (n = 3) and none presented any further participant information to assist diagnosis. Sensitivities ranged from 64% to 80%; specificities ranged from 74% to 85%. In meta-analysis the DOR was 11.9 (95% CI 2.22 to 65.3; 547 lesions and 138 skin cancer cases). Sensitivity and specificity at the average operating point on the SROC curve were 75% (95% CI 49% to 90%) and 79% (95% CI 38% to 96%) respectively. For the three studies that also reported data for the primary target condition (Table 7), sensitivities increased in two due to correct identification of BCCs (Rosendahl 2011; Stanganelli 1998a). Specificity decreased in Carli 2002b due to small sample size and high prevalence of malignancy (20 of 53; 38%) and decreased in Rosendahl 2011 due to the use of a different threshold for the primary target condition 'is this lesion a melanoma?' compared to 'should this lesion be excised?' for the target condition of any lesion requiring excision.

We did not identify any significant difference in accuracy between in-person and image-based evaluations (RDOR 1.70; 95% CI 0.24 to 12.3; P = 0.55).

DISCUSSION

Summary of main results

The included studies evaluated visual inspection in a range of study populations, on an in-person basis and using clinical images, and both with and without the use of published algorithms to assist diagnosis. We observed wide variations in sensitivity and specificity for all definitions of the target condition.

There are five main findings from our review:

1) There is an almost universal problem with poor reporting in the primary studies, hindering attempts to analyse studies according to their position on the clinical pathway and to fully assess sources of heterogeneity and methodological quality.

Fewer than two thirds of in-person evaluations of visual inspection contained enough information to describe where on the clinical pathway participants were assessed. This was particularly the case for studies apparently conducted in referred populations, where almost half of studies neither described participants as 'referred', nor provided any description of participants' prior testing or pathway followed prior to presentation for specialist review. Observer experience and expertise in pigmented lesion diagnosis is likely to affect test accuracy; however, this information was rarely provided in any detail making it difficult to assess any differences in accuracy according to clinician experience. Analyses by reported

observer qualifications and descriptions of observers as 'expert' or 'experienced' showed no significant differences between groups.

In terms of methodological quality, studies were at unclear risk of bias due to poor reporting of key items around participant selection, pre-specification of thresholds used, and timing of diagnosis in relation to reference standard diagnosis. Concern around applicability of studies was almost universally poor due to restricted inclusion of lesions and lack of reproducibility of diagnostic thresholds. Given these limitations and the heterogeneity in various aspects of the primary studies, our results cannot be considered conclusive regarding the accuracy of visual inspection for melanoma diagnosis.

2) Prior testing of participants or study position on the clinical pathway does appear to matter.

Focusing on in-person evaluations that could be clearly positioned on the clinical pathway (Summary of findings), we observed the highest sensitivity (92.4%, 95% CI 26.2% to 99.8%) and lowest specificity (79.7%, 95% CI 73.7% to 84.7%) for the primary target condition of invasive melanoma or atypical intraepidermal melanocytic variants in three datasets from participants with limited prior testing; however, confidence intervals were wide and heterogeneity high, particularly for sensitivity. Data for referred participants suggest that summary sensitivities fall to around 75%, but with much higher specificities (e.g. sensitivity 76.7% (95% CI 61.7% to 87.1%) and specificity 95.7% (95% CI 89.7% to 98.3%) for lesions selected for excision, n = 8 datasets). Sensitivity was higher for equivocal lesion populations but with very wide confidence intervals (84.7%, 95% CI 55.5% to 96.1%) with summary specificity of 89.5% (95% CI 79.5% to 95.0%; 2 datasets). The general trade-off between sensitivity and specificity along the pathway could be due to differences in the spectrum or 'case mix' of included lesions, differences in the definition of a positive test result, or may be linked to variations in observer expertise. Spectrum effects can be observed when tests that are developed further down the referral pathway have lower sensitivity and higher specificity when applied in settings with participants with limited prior testing (Usher-Smith 2016). Classic examples include the use of dipstick tests for detection of urinary tract infection (UTI) (Lachs 1992) and the D-dimer test to detect pulmonary embolism (PE) (Ginsberg 1993). In both studies, as the prior probability of having UTI or PE increases (and so prevalence of disease increased), test sensitivity increased (from 79% to 93% in Ginsberg 1993, and from 58% to 92% in Lachs 1992) while specificities decreased (from 76% to 45% in Ginsberg 1993 and from 77% to 42% in Lachs 1992). However, this direction of effect is not consistent across tests and diseases as Leeflang 2013 clearly demonstrates; the mechanisms in action are often more complex than prevalence alone and can be difficult to identify.

Using disease prevalence as a proxy for disease spectrum, our classification of studies did result in a somewhat lower prevalence of disease (suggesting a wider spectrum of lesion types) in limited prior testing studies (median prevalence 5%, interquartile range (IQR) 3% to 9%) compared to referral settings (median prevalence 15%, IQR 10% to 21%), but with overlapping ranges (2% to 11%, and 1% to 41%, respectively). The lower specificity observed in limited prior testing studies is likely related to the presence of a wider range of benign lesions with similar characteristics to melanoma, leading to more referrals. Observers in primary care are also likely to have a lower threshold for considering benign lesions as possibly malignant due to the risk of missing true cases of melanoma, contributing both to higher sensitivity and a higher false-positive rate. Referred populations on the other hand may have a higher proportion of equivocal or 'difficult-to-diagnose' melanomas that are difficult to identify.

In terms of eligibility criteria, the studies required varying degrees of clinical suspicion of malignancy to include lesions in limited prior-testing populations, ranging from lesions that could not immediately be diagnosed as benign to there being a requirement for a teledermatology second opinion. In referral populations, eligibility was frequently based on lesion excision, the basis or rationale for which was not described. The restriction to lesions deemed to be suitable for excision would decrease specificity, as more obviously benign lesions would be excluded. The spectrum of lesion types in the disease-negative groups also varied across studies, with a number of studies restricting inclusion only to those with melanocytic lesions (such that all benign lesions were benign melanocytic naevi) and others reporting high proportions of other types of skin cancers (BCC or SCC), or of benign keratotic lesions, such as seborrhoeic or actinic keratoses, or of Spitz naevi, which may be difficult to differentiate from melanoma.

3) Visual inspection alone is not sufficiently sensitive for the detection of melanoma, and there is no clear evidence that accuracy is improved by the use of any named or published algorithm to assist diagnosis in all settings.

Test sensitivity was greater than 90% (i.e. fewer than 1 in 10 melanomas missed) in only six of the 28 in-person-based evaluations of the primary target condition, and confidence intervals for the pooled estimates were wide, raising the question of whether visual inspection can be relied on to rule out the presence of melanoma. Applying the sensitivity and specificity estimates for the limited prior testing studies cited above to a hypothetical cohort of 1000 lesions at disease prevalence of 4%, 9%, and 16% (see Summary of findings) shows that on average, visual inspection would miss 3, 7 or 12 melanomas, with 195, 185 and 171 false-positive results (potentially leading to unnecessary excisions or lesion referral or follow-up depending on the anticipated clinical action following a positive result). The wide confidence intervals however mean that the number of melanomas missed could range from between 0 and 118, with false-positives from 129 to 252. For a cohort of 1000 lesions in a referred population at prevalence of 4%, 9%, and 16% (Summary of findings), the pooled sensitivity of 76.7% and specificity 95.7% translate to 9, 21, and 37 melanomas missed on average (range: 5 to 61) and 41, 39, and 36 false-positive results (range: 14 to 99).

The evidence to support the use of available algorithms to assist visual inspection was limited, and results are likely to be confounded by patient spectrum and observer experience. We also observed considerable variation in definitions of test positivity across studies that did not report using any algorithm, that is, where observer diagnosis was based on observers' own interpretation of lesion characteristics. Where reported, visual inspection was considered to be positive for observers 'correct diagnosis of melanoma', 'suspicion of malignancy', or 'selection for excision', each of which is likely to result in varying proportions of test-positive or test-negative for any given population.

Nevertheless, covariate investigations for the primary analysis across all study settings suggested no difference in accuracy according to the reported use of any named or published algorithm to assist diagnosis. This result was supported by limited subgroup analysis according to algorithm used. Only one eligible study directly compared the accuracy of visual inspection with and without the use of an algorithm (Collas 1999); however, the study authors developed their own new algorithm for the study and found sensitivity to be higher without the use of the algorithm. Comparing different algorithms, McGovern 1992 reported highest sensitivities from the BCD algorithm (any one characteristic present) and the original seven-point checklist (at least two characteristics present). Current guidelines in the UK support the use of the revised seven-point checklist in primary care (NICE 2015a). A number of studies assessing the revised seven-point checklist algorithm did not meet the stringent inclusion criteria for our review (Healsmith 1994; Higgins 1992; Osborne 1999; Walter 2013); however, the single eligible study using the revised seven-point checklist as part of a large randomised controlled trial reported high sensitivity (94%) when used by GPs (Walter 2012).

4) The definition of the target condition has an effect on diagnostic accuracy.

Results from studies reporting data for more than one definition of the target condition show that sensitivity in particular is affected by the inclusion of, and percentage of, melanoma in situ and BCC lesions considered disease-positive. The direction of effect depends on observers' ability to correctly identify these lesions as malignant. It is likely that similar effects have an impact on results observed across all included studies. Clear identification of the target condition was not provided in 11 of the 28 datasets included in our primary analyses, so that the inclusion of melanoma in situ lesions as disease-positive was assumed on the basis that the disease-positive group was described as 'melanoma' and not as 'invasive melanoma' or 'malignant melanoma'. Of those studies that clearly reported including in situ lesions, the percentage of the disease-positive group (invasive melanoma and atypical intraepidermal melanocytic variants) described as being in situ ranged from 10% to 50%. Where studies included other invasive skin cancers (mainly BCCs or SCCs) in the study population (lesions considered disease-negative for detection of the primary target), we attempted to class any that were correctly identified by observers as malignant as 'true negative' results as opposed to 'false-positive' (thereby increasing observed specificities), on the basis that removal of any skin cancer in the attempt to identify melanomas would not be a negative consequence of the test. Our ability to reclassify lesions relied on studies providing a disaggregation of test results according to final lesion classification and was not always possible, particularly when invasive SCCs were not separated from 'in situ' lesions such as Bowen's disease.

5) There are substantial differences in diagnostic accuracy between in-person and image-based assessments.

Accuracy was much lower and reporting was poorer for evaluations of a diagnosis based on the interpretation of clinical images as opposed to in-person evaluations. Other than possible differences in patient spectrum between in-person and image-based studies, one possible explanation for the observed difference is that even using the highest quality clinical image, a remote assessment is not equivalent to a physical, face-to-face, patient-to-clinician interaction, which will include patient history-taking as well as a total body examination. We were unable to examine any impact from history-taking over and above inspection of the lesion itself; however, history-taking and in particular, assessment of and knowledge of patients' other lesions could have a significant impact on the decision as to whether or not a patient has melanoma (Aldridge 2013; Grob 1998). Subtle differences in assessing the lesion shape and colour can be done in an in-person consultation, for example, by stretching the lesion in the axis perpendicular to the skin creases, which may distort the lesion shape, and by altering the light intensity and direction used during lesion inspection. Palpation of the lesion (and regional lymph nodes) is also possible during in-person examination. The fact that image quality is likely to vary between studies, the time taken to review each image is likely to vary, and the considerable variation in supplementary information provided to observers (ranging from no clinical information, to clinical details regarding patient age, gender or lesion site and information on lesion change over time) will have further contributed to variation in accuracy and lower accuracy estimates in comparison to in-person evaluations. Furthermore, the diagnostic context may have a key influence on observer decisions. In a face-to-face diagnostic encounter and for the examination of lesion images for a teledermatology consultation, the clinicians concerned know that their assessment has a direct consequence on patient management and potentially on patient outcomes. The image-based evaluations included in our primary analysis however were not conducted for teledermatology purposes, but were studies using lesion images to compare accuracy between clinical-image diagnosis and dermoscopic-image diagnosis, or to compare observer or algorithm performance, for example. Observers would have been aware that their assessment of the lesion image was done in an experimental setting, and would not have an impact on patients; this could potentially have affected interpretation.

Strengths and weaknesses of the review

The strengths of our review include an in-depth and comprehensive electronic literature search, systematic review methods including double extraction of papers by both clinicians and methodologists, and contact with study authors to allow study inclusion or clarify data. In order to estimate test accuracy in different study populations, we adopted a clear analysis structure according to approach to diagnosis, the definition of the target condition, and the patient pathway. We undertook a detailed and replicable analysis of methodologic quality.

In comparison to other available systematic reviews, our review extends the time period searched for eligible studies to August 2016 (from 2007 in Vestergaard 2008 and from March 2015 in Harrington 2017), and we include all eligible studies regardless of availability of a direct comparison with dermoscopic examination (as required in Vestergaard 2008) or requirement for an algorithm or clinical prediction rule to be included (Harrington 2017). Our stringent application of review inclusion criteria meant that we excluded several otherwise eligible studies. For example, we excluded those reporting accuracy data for 'clinical diagnosis', where dermoscopy may or may not have been used to assist diagnosis, on the basis that the contribution of visual inspection of the lesion could not be discerned.

We also excluded from our review studies evaluating eligible algorithms (that were included in Harrington 2017), due to lack of data to construct a 2x2 contingency table, the serial use of the algorithm in the context of lesion follow-up, or use of inadequate reference standards. Without these restrictions, the observed data would likely have been considerably more heterogeneous and of poorer methodological quality. At the same time, our inclusion of all studies reporting data for visual inspection meant that we were able to make an overall assessment of observer accuracy, regardless of the use of a named algorithm. Harrington and colleagues rightly point out that lower sensitivity associated with the use of a clinical prediction rule "should not prevent [its] use unless usual decisions, made without the rule, are demonstrably better"; however, unless the accuracy of 'usual decisions' is examined, any benefit from the use of an algorithm cannot be established.

The main concerns for the review are a result of the poor reporting of primary studies, in particular forcing some assumptions to be made to allow studies to be split by pathway and in separating studies by the different definitions of the target condition. Our inability to clearly separate studies by pathway is of real concern given the evidence for the effect on accuracy according to the spectrum or case-mix of included participants (Lachs 1992; Leeflang 2013; Moons 1997).

Finally, observer expertise is key for any diagnostic process based on visual inspection, with both non-analytical pattern recognition (implicit identification) and analytical pattern recognition (using more explicit 'rules' based on conscious analytical reasoning) employed to varying extents between clinicians, according to factors such as experience and familiarity with the diagnostic question (Norman 2009). A lack of clear reporting of observer training and experience made analysis difficult.

Applicability of findings to the review question

Varying definitions of the eligible study populations and lack of clarity regarding the patient pathway and any prior testing may restrict the extent to which our findings are applicable to the clinical setting. Varying definitions of test positivity and lack of reproducibility of diagnostic thresholds, variability in the use of published algorithms, and in observer qualifications and experience, further restrict the transferability of results to a clinical setting.

AUTHORS' CONCLUSIONS

Implications for practice

Visual inspection is an essential, fundamental component of the assessment of a suspicious skin lesion; however, the evidence suggests that melanomas will be missed if visual inspection is used on its own. The evidence to support its accuracy in the range of settings in which it is used is both flawed and poorly reported, resulting in an inability to produce meaningful summary results and clear pointers as to where visual inspection is most useful. Overall, the use of published algorithms to assist diagnosis does not appear to improve accuracy; however, neither is there sufficient evidence to suggest that the 'no algorithm' approach should be preferred in all settings, for example, for training junior staff. Further investigation may lend support to the theory that expert observers are more reliant on non-analytical pattern recognition, while attempts to assist analytical pattern recognition are of more benefit for less experienced or more generalist observers.

Implications for research

Despite the vast volume of research that has been funded to evaluate visual inspection, further prospective evaluation of the added value of established algorithms according to the prior testing or diagnostic difficulty of lesions may be warranted. Prospective recruitment of consecutive series of participants and with systematic follow-up of non-excised lesions to avoid over-reliance on a histological reference standard would allow results to be more generalisable to routine practice. A clear identification of the level of training and experience required to achieve good results is also required. Any future research study needs to be clear about the diagnostic pathway followed by study participants prior to study enrolment, and should conform to the updated Standards for Reporting of Diagnostic Accuracy (STARD) guideline (Bossuyt 2015).

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Usher-Smith JA, Sharp SJ, Griffin SJ. The spectrum effect in tests for risk prediction, screening, and diagnosis. *BMJ* 2016;**353**:i3139. DOI: 10.1136/bmj.i3139

Vestergaard 2008
Vestergaard ME, Macaskill P, Holt PE, Menzies SW. Dermoscopy compared with naked eye examination for the diagnosis of primary melanoma: a meta-analysis of studies performed in a clinical setting. *British Journal of Dermatology* 2008;**159**(3):669–76. [PUBMED: 18616769]

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Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Annals of Internal Medicine* 2011;**155**(8):529–36. [PUBMED: 22007046]

Yagerman 2014
Yagerman SE, Chen L, Jaimes N, Dusza SW, Halpern AC, Marghoob A. 'Do UC the melanoma?' Recognising the importance of different lesions displaying unevenness or having a history of change for early melanoma detection. *Australasian Journal of Dermatology* 2014;**55**(2):119–24. [PUBMED: 24548383]

Zalaudek 2006
Zalaudek I, Argenziano G, Soyer HP, Corona R, Sera F, Blum A, et al. Dermoscopy Working Group. Three-point checklist of dermoscopy: an open Internet study. *British Journal of Dermatology* 2006;**154**(3):431–7. [PUBMED: 16445771]

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Dinnes 2015a
Dinnes J, Matin RN, Moreau JF, Patel L, Chan SA, Wong KY, et al. Tests to assist in the diagnosis of cutaneous melanoma in adults: a generic protocol. *Cochrane Database of Systematic Reviews* 2015, Issue 10. DOI: 10.1002/14651858.CD011902

Dinnes 2015b
Dinnes J, Wong KY, Gulati A, Chuchu N, Leonardi-Bee J, Bayliss SE, et al. Tests to assist in the diagnosis of keratinocyte skin cancers in adults: a generic protocol. *Cochrane Database of Systematic Reviews* 2015, Issue 10. DOI: 10.1002/14651858.CD011901

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Argenziano 2006

Study characteristics	
Patient sampling	**Study design:** RCT allocating primary care physicians to use either VI alone or VI plus dermoscopy (only excised lesions can be included for each arm) **Data collection**: prospective **Period of data collection**: May 2003-September 2004 **Country**: Italy and Spain
Patient characteristics and setting	**Inclusion criteria**: patients asking for screening or exhibiting ≥ 1 skin tumours as seen during routine physical examination (patient-finding screening) were considered for inclusion; those undergoing excision were included in this review (i.e. those deemed sufficiently suspicious by the expert evaluation). PCPs were invited to participate in the trial; only those who attended the training sessions and who then screened patients and referred them to the PLCs were randomised **Setting**: primary **Prior testing**: no prior testing **Setting for prior testing:** N/A **Exclusion criteria:** NR **Sample size (participants)**: number eligible: 3271 screened; 1325 participants allocated to 'naked eye' observation and 1197 participants allocated to dermoscopy observation; number included: 162 received histology after expert evaluation at the PLC **Sample size (lesions):** 85 in VI arm and 77 in dermoscopy arm underwent excision **Participant characteristics**: based on full sample: mean age 40, range 2-90 (VI group)/ 41, range 3-94 (dermoscopy group). Male 498 (38%): VI group/451 (38%) dermoscopy **Lesion characteristics**: NR
Index tests	**VI**: ABCD (control arm of RCT comparing naked eye examination to naked eye plus dermoscopy) **Method of diagnosis:** in-person diagnosis **Prior test data:** N/A in-person diagnosis **Diagnostic threshold**: qualitative NR; described in intro as: simple morphologic features summarized by the asymmetry, border irregularity, colour variegation, and diameter 5 mm (ABCD) **Diagnosis based on**: average (n = 37) **Observer qualifications**: primary care physicians **Experience in practice**: not described **Experience with index test**: not described **Other detail**: pre-randomisation all participating PCPs underwent training in ABCD rule for clinical diagnosis and 3-point checklist for dermoscopy **Dermoscopy:** evaluated in intervention arm of trial only
Target condition and reference standard(s)	**Reference standard:** histological diagnosis alone Details: all lesions considered suggestive of skin cancer at the PLC were excised and subsequently diagnosed histopathologically. Equivocal lesions by histopathologic examination were reviewed by a second independent pathologist and a final diagnosis made. Disease positive: 92 malignant tumours; disease negative: 70 benign tumours **Target condition (final diagnoses)**

	Melanoma (in situ and invasive, or NR): 12; BCC: 66; cSCC: 14 SK: 13; MN 51; other: 6		
Flow and timing	**Excluded participants**: data can only be extracted for those with histology (i.e. participants considered to have lesions suggestive of skin cancer); remainder had expert diagnosis (not included in the final 2x2 data extracted) **Time interval to reference test**: NR		
Comparative	RCT examining effect of making dermoscopy available to primary care practitioners		
Notes	-		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Are the included patients and chosen study setting appropriate?	No		
Did the study avoid including participants with multiple lesions?	Unclear		
		Unclear	**High**
DOMAIN 2: Index Test Visual Inspection - in-person			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold			

or algorithm interpreted without knowledge of the results of the others?			
Was the test applied and interpreted in a clinically applicable manner?	No		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		
Was the test interpretation carried out by an experienced examiner?	Unclear		
		Low	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		

Argenziano 2006 (*Continued*)

Were all patients included in the analysis?	No		
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?			
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			
		High	

Barzegari 2005

Study characteristics	
Patient sampling	**Study design**: CS **Data collection**: NR **Period of data collection**: NR **Country**: Iran
Patient characteristics and setting	**Inclusion criteria**: PSLs with a clinical diagnosis of melanocytic lesion ≤ 15 mm diameter referred to dermatology clinic for diagnostic evaluation or cosmetic reasons **Setting**: secondary (general dermatology) **Prior testing**: clinical suspicion of malignancy without dermatoscopic suspicion; patient request for evaluation/excision **Setting for prior testing**: NR **Exclusion criteria**: none reported **Sample size (participants)**: number included: 91 **Sample size (lesions)**: number included: 122 **Participant characteristics**: mean age 32.3 (6-94 years); male: 30; 33% **Lesion characteristics**: NR
Index tests	**VI**: no algorithm **Method of diagnosis:** in-person diagnosis **Prior test data:** N/A in-person diagnosis **Diagnostic threshold**: qualitative melanoma likely (i.e. melanoma first in list of considered diagnoses)/ melanoma possible (melanoma one of a number of diagnoses) **Diagnosis based on**: consensus (2 observers); n = 2 **Observer qualifications**: dermatology registrar (dermatology resident (3rd year)); dermatologist

	Experience in practice: mixed experience (low and high experience combined) **Experience with index test**: mixed (low and high experience combined)		
Target condition and reference standard(s)	**Reference standard**: histological diagnosis alone Disease positive: 6; disease negative: 116 **Target condition (final diagnoses)** Melanoma (invasive): 3; melanoma (in situ): 3 SK: 2; benign naevus: 104; dysplastic naevus 7 DF, 1 AK		
Flow and timing	**Excluded participants**: none **Time interval between index and reference**: unclear **Time interval between index test(s)**: consecutive		
Comparative			
Notes	-		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Are the included patients and chosen study setting appropriate?	Unclear		
Did the study avoid including participants with multiple lesions?	No		
		Low	**High**
DOMAIN 2: Index Test Visual Inspection - in-person			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		

Barzegari 2005 (*Continued*)

If a threshold was used, was it pre-specified?	Unclear		
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
Was the test applied and interpreted in a clinically applicable manner?	No		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpretation carried out by an experienced examiner?	Unclear		
		Unclear	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**Unclear**
DOMAIN 4: Flow and Timing			

Barzegari 2005 (*Continued*)

Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?			
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?	No		
		Unclear	

Benelli 1999

Study characteristics	
Patient sampling	**Study design**: CS **Data collection**: prospective **Period of data collection**: 1 September1997-30 September 1998 **Country**: Italy
Patient characteristics and setting	**Inclusion criteria**: all PSLs observed and excised at the dermatologic surgery department **Setting**: dermatologic surgery department **Prior testing**: selected for excision (no further detail) **Setting for prior testing**: dermatologic surgery department **Exclusion criteria**: none reported **Sample size (participants):** NR **Sample size (lesions)**: number included: 401 **Participant characteristics:** NR **Lesion characteristics**: melanoma thickness: 6 *in situ*; 42 < 0.75 mm thick, 80 0.76-1.5 mm thick, 4 1.5-4 mm thick (mean 0.60 mm, median 0.55 mm, max 1.9 mm, min 0.10 mm, SD 0.45)

Benelli 1999 (*Continued*)

Index tests	**VI**: ABCDE **Method of diagnosis:** in-person diagnosis **Prior test data**: lesions assessed by both dermatologists clinically and dermoscopically **Diagnostic threshold**: data given for accuracy of each potential score (1-5); score estimation described in detail **Diagnosis based on**: consensus (2 observers); n = 2 **Observer qualifications**: dermatologist **Experience in practice**: not described **Experience with index test**: not described **Dermoscopy** 7FFM also assessed by same observers
Target condition and reference standard(s)	**Reference standard**: histological diagnosis alone Disease positive: 60 (15%) lesions; disease negative: 340 (non melanoma) + 1 BCC **Target condition (final diagnoses)** Melanoma (invasive): 54 (13.5%); melanoma (in situ): 6 (1.5%); BCC: 1 (0.4%) SK: 1 (0.4%); MN: 316; epithelioid and/or spindle cell naevi: 18 (4.5%); LS: 5 (1.2%)
Flow and timing	**Excluded participants**: NR **Time interval to reference test**: same day
Comparative	Blinding between tests: Clinical and dermoscopic evaluations made in-person by 2 dermatologists prior to excision Time interval between index test(s): same day
Notes	-

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Are the included patients and chosen study setting appropriate?	No		
Did the study avoid including participants with multiple lesions?	Unclear		

Benelli 1999 (*Continued*)

		Unclear	**High**
DOMAIN 2: Index Test Visual Inspection - in-person			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	No		
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
Was the test applied and interpreted in a clinically applicable manner?	No		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		
Was the test interpretation carried out by an experienced examiner?	Unclear		
		High	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes		

Benelli 1999 (*Continued*)

Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?			
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			
		Low	

Benelli 2001

Study characteristics	
Patient sampling	**Study design**: unclear **Data collection**: retrospective image selection/prospective interpretation **Period of data collection**: NR - only dates of training course and agreement study given (April-May 1999) **Country**: Italy
Patient characteristics and setting	**Inclusion criteria**: slides of pigmented skin tumours were selected for evaluation during a training course on dermoscopy. Lesions not located on head, palms or soles; histological slide available

	Setting: training images; study authors' institution. Institute of Dermatologic Sciences, University of Milan **Prior testing**: slides of pigmented skin tumours were selected for evaluation during a training course on dermoscopy **Setting for prior testing**: unspecified **Exclusion criteria**: none reported **Sample size (participants)**: NR **Sample size (lesions)**: number included: 49 (paper reports 50 but only 49 accounted for in text) **Participant characteristics**: none reported **Lesion characteristics**: none reported
Index tests	**VI**: ABCDE **Method of diagnosis**: clinical photographs **Prior test data**: no further information used **Diagnostic threshold:** ABCDE Score ≥ 2; presence of 2 criteria; ABCDE score ≥ 3; presence of 3 criteria. All criteria described in full **Diagnosis based on**: single (n = 1); average (n = 65; attending 1/3 courses in dermoscopy held to inform dermatologists about a new dermatoscopic diagnostic method (7FFM)) **Observer qualifications**: dermatologists **Experience in practice**: expert author; not described for participating dermatologists **Experience with dermoscopy**: expert author; prior experience not described for participating dermatologists; all underwent dermoscopy training for study purposes **Dermoscopy:** 7FFM; ABCDE also evaluated in study
Target condition and reference standard(s)	**Reference standard**: histological diagnosis alone Disease positive: 12/49 melanomas (paper reports 50 but only 49 accounted for in text) **Target condition (final diagnoses)** Melanoma (invasive): 10; melanoma (in situ): 2; BCC: 2 pigmented BCC 3 seborrhoeic keratoses: 2; pigmented BCC: 1; blue nevus: 2; angiokeratoma: 5; Spitz nevus: 5; junctional naevi 9 compound naevi, 10 naevi undergoing regression
Flow and timing	**Excluded participants**: none reported **Time interval to reference test**: unclear
Comparative	Blinding between tests: Clinical images interpreted in the morning and dermoscopic images in the afternoon Time interval between index test(s): image capture NR
Notes	-

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		

Was a case-control design avoided?	Unclear		
Did the study avoid inappropriate exclusions?	Unclear		
Are the included patients and chosen study setting appropriate?	No		
Did the study avoid including participants with multiple lesions?	Unclear		
		Unclear	**High**
DOMAIN 2: Index Test Visual inspection - image-based			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
Was the test applied and interpreted in a clinically applicable manner?	No		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		
Was the test interpretation carried out by an experienced examiner?	Yes		
		Low	**High**
DOMAIN 3: Reference Standard			

Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?			
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			
		Unclear	

Bono 1996

Study characteristics			
Patient sampling	**Study design**: unclear **Data collection**: NR **Period of data collection**: March 1993-October 1994 **Country**: Italy		
Patient characteristics and setting	**Inclusion criteria**: PSLs at the Instituto Nazionale Tumori of Milan **Setting**: specialist unit (skin cancer clinic/PLC) Instituto Nazionale Tumori of Milan **Prior testing**: NR **Setting for prior testing**: NR **Exclusion criteria**: none reported **Sample size (participants)**: number eligible: 45 **Sample size (lesions)**: number eligible: 54/ number included: 43 **Participant characteristics:** NR **Lesion characteristics**: site - face/ears: 3 (6%)/trunk: 39 (72%)/limbs: 12 (22%); 10 MM ≤ 1 mm depth; median size: 10 mm (4 mm-40 mm)		
Index tests	**VI**: no algorithm **Method of diagnosis:** in-person diagnosis **Prior test data:** N/A in-person diagnosis **Diagnostic threshold**: NR; 'clinical diagnosis' **Diagnosis based on**: single observer; n = NR **Observer qualifications:** treating surgeon **Experience in practice**: not described **Experience with index test**: not described		
Target condition and reference standard(s)	**Reference standard**: histological diagnosis Disease positive: 18; disease negative: 25 Expert opinion: disease negative: 11 **Target condition (final diagnoses)** Melanoma (in situ and invasive, or NR): 18 Mild/moderate dysplasia: 8 dysplastic naevi Benign naevus: 17 common MN		
Flow and timing	**Excluded participants**: only 43 lesions had complete clinical and histological information. 11 lesions not surgically removed had only clinical diagnosis (benign) and were not included in the final accuracy analysis **Time interval to reference test**: NR **Time interval between index test(s)**: NR		
Comparative			
Notes	-		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**

Bono 1996 (*Continued*)

DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Unclear		
Did the study avoid inappropriate exclusions?	Unclear		
Are the included patients and chosen study setting appropriate?	Unclear		
Did the study avoid including participants with multiple lesions?	No		
		Unclear	**High**
DOMAIN 2: Index Test Visual Inspection - in-person			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Unclear		
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
Was the test applied and interpreted in a clinically applicable manner?	Yes		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpretation carried out by an experienced examiner?	Unclear		

Bono 1996 (*Continued*)

		Unclear	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	No		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Expert opinion (with no histological confirmation) was not used as a reference standard	No		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		High	**High**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	No		
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?	Yes		
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms			

Bono 1996 (*Continued*)

1 month or less?			
		High	

Bono 2002a

Study characteristics	
Patient sampling	**Study design**: CS **Data collection**: prospective **Period of data collection**: June 1998-March 2000 **Country**: Italy **Test set derived**: a training set was separately derived using data obtained from 237 previously studied lesions (Farina 2000)
Patient characteristics and setting	**Inclusion criteria**: cutaneous pigmented lesions with clinical and/or dermatoscopic features that suggested a more or less important suspicion for CM **Setting**: specialist unit (skin cancer clinic/PLC) **Prior testing**: clinical and/or dermatoscopic suspicion **Setting for prior testing**: specialist unit (skin cancer clinic/PLC) **Exclusion criteria**: location/site of lesion. Awkwardly situated lesions, e.g. interdigital space, ears, nose or eyelids. Lesions on scalp excluded due to hair interference with reflectance. Lesion size, obvious large, thick melanomas **Sample size (participants)**: number included: 298 **Sample size (lesions)**: number included: 313 **Participant characteristics**: mean age: 40 years (10-86 years); male: 122; 41% **Lesion characteristics**: lesion site: head/neck: 3%; trunk: 61%; limbs: 36%; thickness $\leq$ 1 mm: 70% (46/66); for 55 invasive MM: median thickness 0.64 mm, range 0.17-3.24 mm. Median diameter: 11 mm (3-31 mm)
Index tests	**VI**: no algorithm (training in the unit based on ABCD but subjective experience of the clinician used for diagnosis) **Method of diagnosis:** in-person diagnosis **Prior test data**: same clinician undertook clinical diagnosis and diagnosis using dermoscopy **Diagnostic threshold**: clinical diagnostic criteria based on subjective experience; emphasised lesion colour over dimensions. Diagnosis of suspect CM made when the level of suspicion was "roughly 50% or more". ABCD criteria have been the basis of training at the unit, but is not implemented in diagnosis; preferred emphasis on colour rather than dimensional character **Diagnosis based on**: single observer; (n = 1) **Observer qualifications**: surgical oncologists **Experience in practice**: high experience or 'Expert'; over 5 years **Dermoscopy:** also evaluated in same study (no algorithm)
Target condition and reference standard(s)	**Reference standard**: histological diagnosis alone **Target condition (final diagnoses)** Melanoma (invasive): 55; Melanoma (in situ): 11; BCC: 6 'Benign' diagnoses: 241; 151 compound naevus, 24 junctional naevus, 12 dermal naevus, 12 LS, 10 dysplastic naevus, 8 spindle-cell naevus, 8 SK, 5 blue naevus, 3 Spitz naevus, 8 other

Flow and timing	**Excluded participants**: NR **Interval between index and reference**: NR		
Comparative	Same clinician undertook both diagnoses (in-person) Time interval between index test(s): Appears consecutive but not fully clear		
Notes	-		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
Are the included patients and chosen study setting appropriate?	No		
Did the study avoid including participants with multiple lesions?	Yes		
		High	**High**
DOMAIN 2: Index Test Visual Inspection - in-person			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			

Was the test applied and interpreted in a clinically applicable manner?	Yes		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpretation carried out by an experienced examiner?	Yes		
		Low	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		

Bono 2002a (*Continued*)

If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?			
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			
		Unclear	

Bono 2002b

Study characteristics	
Patient sampling	**Study design**: CS **Data collection**: prospective **Period of data collection**: December 2000 and August 2001 **Country**: Italy
Patient characteristics and setting	**Inclusion criteria**: consecutive cutaneous pigmented lesions that were ≤ 6 mm in diameter and required surgical biopsy for diagnosis based on clinical or dermoscopic suspicion of CMM **Setting**: specialist unit (skin cancer clinic/PLC) **Prior testing**: clinical and/or dermatoscopic suspicion **Setting for prior testing**: NR **Exclusion criteria:** lesion size > 6 mm; non-pigmented **Sample size (participants)**: number eligible: 349/number included: 157 **Sample size (lesions)**: number eligible: 375/number included: 161 **Participant characteristics**: mean age 38 years (14-82); male: 61 (39%) **Lesion characteristics**: site: head/neck: 14 (9%); trunk: 88 (55%); limbs: 59 (36%) **Lesion size:** median: 5 mm (1 mm-6 mm)
Index tests	**VI**: no algorithm (ABCD criteria have been the basis of training at the unit, but is not implemented in diagnosis; preferred emphasis on colour rather than dimensional character) **Method of diagnosis:** in-person diagnosis **Prior test data:** N/A, in-person diagnosis **Other test data**: dermoscopy evaluated in same study by same observer(s) **Diagnostic threshold**: a diagnosis of suspect CM is made when the level of suspicion is roughly 50% or more; lesions at a lower index of suspicion were considered benign for the purposes of this study **Diagnosis based on**: single observer diagnostic criteria based on the subjective experience of the single clinician examining the pigmented lesion (n = 2)

	Observer qualifications: surgical oncologists **Experience in practice**: high experience or 'Expert'; observers described as "expert in the recognition of pigmented lesions" **Other detail**: diagnostic criteria were based on the subjective experience of the single clinician examining the pigmented lesion, although the ABCD criteria have been the basis of training at the unit, they did not consider the ABCD mnemonic an essential formula for diagnosis of CM. They did not take into consideration the dimensional character and attributed great importance to the colour of a given lesion **Dermoscopy:** performed by the same 2 clinicians who firstly made and registered the clinical diagnosis
Target condition and reference standard(s)	**Reference standard**: histological diagnosis alone Disease positive: 13 CM; disease negative: 148 **Target condition (final diagnoses)** Melanoma (invasive): 10; melanoma (in situ): 3; BCC: 2 (1.2%) Mild/moderate dysplasia: 26 (16.1%); SK: 4 (2.5%); benign naevus: compound nevus 57 (35.4%) , junctional nevus 38 (23.6%), spindle-cell nevus 6 (3.7%), Spitz nevus 5 (3.1%), blue nevus 2 (1. 2%), other 6 (3.7%), LS 2 (1.2%)
Flow and timing	**Excluded participants**: none reported **Time interval to reference test**: NR
Comparative	Dermoscopy performed by the same two clinicians who firstly made and registered the clinical diagnosis Time interval between index test(s): appears consecutive
Notes	-

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Are the included patients and chosen study setting appropriate?	No		
Did the study avoid including participants with multiple lesions?	Yes		

Bono 2002b (*Continued*)

		Low	High
DOMAIN 2: Index Test Visual Inspection - in-person			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
Was the test applied and interpreted in a clinically applicable manner?	Yes		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpretation carried out by an experienced examiner?	Yes		
		Low	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes		

Bono 2002b (*Continued*)

Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?			
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			
		Unclear	

Bono 2006

Study characteristics	
Patient sampling	**Study design**: CS **Data collection**: retrospective **Period of data collection**: January 2003-December 2004 **Country**: Italy
Patient characteristics and setting	**Inclusion criteria**: consecutive patients with PSLs with a maximum diameter of ≤ 3 mm undergoing excision. The decision for diagnostic excision was based on clinical and/or dermoscopic features suggesting a more or less important suspicion for CM

	Setting: specialist unit (skin cancer clinic/PLC) Istituto Nazionale Tumori of Milan **Prior testing**: clinical and/or dermatoscopic suspicion **Setting for prior testing**: specialist unit (skin cancer clinic/PLC) **Exclusion criteria:** lesion size > 3 mm **Sample size (participants)**: number eligible: 204/number included: 204 **Sample size (lesions)**: number eligible: 206/number included: 206 **Participant characteristics**: median age: 40 (6-74); male: 71 (35%) **Lesion characteristics**: head/neck: 8 (4%); trunk: 84 (41%); limbs: 114 (55%). Median size: 2 mm (1 mm-3 mm)
Index tests	**VI**: no algorithm **Method of diagnosis:** in-person diagnosis **Prior test data:** N/A, in-person diagnosis **Other test data**: dermoscopy evaluated in same study by same observer(s) **Diagnostic threshold**: a diagnosis of suspicious CM is made when the level of suspicion is roughly 50% or more; lesions at a lower index of suspicion were considered not CM **Diagnosis based on**: single observer; n = 1 **Observer qualifications**: NR (assumed Oncologist as per Bono 2002a and Bono 2002b); "single clinician examining the pigmented lesion" **Experience in practice**: not described **Experience with dermoscopy**: not described **Dermoscopy:** evaluated in same study; Menzies criteria **Any other detail:** ABCD criteria have been the basis of training at the unit, but is not implemented in diagnosis; preferred emphasis on colour rather than dimensional character
Target condition and reference standard(s)	**Reference standard**: histological diagnosis alone Details: the slides were evaluated according to widely accepted criteria for the histopathological diagnosis of the various pigmented lesions. Disease positive: 23; disease negative: 183 **Target condition (final diagnoses)** Melanoma (invasive): 19 (9.2%); melanoma (in situ): 4 (2.0%) Mild/moderate dysplasia: dysplastic naevus 10 (4.9%); junctional naevus 76 (36.9%); compound naevus 50 (24.3%); dermal naevus 12 (5.8%); blue naevus 11 (5.3%); reed naevus 7 (3.4%); Spitz naevus 3 (1.5%); halo naevus 3 (1.5%); LS 7 (3.4%); other 4 (1.9%)
Flow and timing	**Excluded participants:** none **Time interval to reference test**: NR
Comparative	Sibngle observer performed both tests Time interval between index test(s): not reported
Notes	-

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			

Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Are the included patients and chosen study setting appropriate?	No		
Did the study avoid including participants with multiple lesions?	Yes		
		Low	**High**
DOMAIN 2: Index Test Visual Inspection - in-person			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
Was the test applied and interpreted in a clinically applicable manner?	Yes		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpretation carried out by an experienced examiner?	Unclear		
		Low	**High**

Bono 2006 (*Continued*)

DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?			
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			

Bono 2006 (*Continued*)

		Unclear	

Bourne 2012

Study characteristics	
Patient sampling	**Study design**: CS **Data collection**: retrospective image selection/prospective interpretation **Period of data collection**: 1 June-6 July 2009 **Country**: Australia
Patient characteristics and setting	**Inclusion criteria**: all skin lesions consecutively excised at a skin cancer practice to exclude skin cancer and common lesions assessed as clearly benign and not biopsied were included **Setting**: primary **Prior testing**: clinical and/or dermatoscopic suspicion. Prior testing to assemble the test set occurs in secondary care by an experienced skin cancer doctor, then the images are tested on primary care professionals **Setting for prior testing**: specialist unit (skin cancer clinic/PLC) **Exclusion criteria**: clinically obvious BCCs that could be easily diagnosed without dermoscopy were not included in the collection set **Sample size (participants)**: number eligible: 46/number included: 46 **Sample size (lesions)**: number eligible: 50/number included: 50 **Participant characteristics**: mean age: 58 (30-60); male: 22 **Lesion characteristics:** face = 8; neck = 1; chest = 3; back = 21; shoulder = 2; arm = 3; thigh = 4; leg = 7; foot plantar = 1
Index tests	**VI**: no algorithm **Method of diagnosis**: clinical photographs **Prior test data**: no further information used; image assessments were done on 4 occasions, each time using a different diagnostic approach **Diagnostic threshold**: NR, clinicians provided with Excel answer sheets for each method listing the various criteria used in that algorithm but no algorithm was cited for VI **Diagnosis based on**: average (n = 4) **Observer qualifications:** 3 GPs and 1 clinical nurse **Experience in practice**: mixed; described as varying levels of dermatoscopic experience **Dermoscopy:** evaluated in same study; 3-point rule; Menzies criteria
Target condition and reference standard(s)	**Reference standard**: histological diagnosis plus other Histopathological examination (n = 46); expert diagnosis as benign (n = 3); digital follow-up (n = 1) **Target condition (final diagnoses)** Melanoma (invasive): 1; melanoma (in situ): 7; BCC: 6; lentigo maligna 1 SK: 5. 'Benign' diagnoses: banal nevus 10, blue naevus 1, nevus and SK/solar lentigo collision 3, solar lentigo 4, LPLK 4, DF 1, psoriasis 1, solar keratosis 2, intraepidermal carcinoma 3, regressed keratoacanthoma 1

Flow and timing	Excluded participants: as 2 of the methods (Menzies and 3-point checklist) related to only pigmented lesions, we excluded the 5 non-pigmented specimens in the set of 50 from the contingency tables for these methods Time interval to reference test, quote: "all skin lesions consecutively excised to exclude skin cancer were recorded"
Comparative	
Notes	-

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Are the included patients and chosen study setting appropriate?	No		
Did the study avoid including participants with multiple lesions?	Yes		
		Unclear	**High**
DOMAIN 2: Index Test Visual inspection - image-based			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Unclear		
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted with-			

out knowledge of the results of the others?			
Was the test applied and interpreted in a clinically applicable manner?	No		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpretation carried out by an experienced examiner?	Unclear		
		Unclear	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Expert opinion (with no histological confirmation) was not used as a reference standard	No		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**High**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	No		

If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?	Unclear		
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?	Yes		
		High	

Carli 2002a

Study characteristics	
Patient sampling	**Study design**: CS **Data collection**: prospective for clinical examination and in vivo dermoscopy; retrospective image selection/prospective interpretation for ex vivo dermoscopic evaluation **Period of data collection**: June 1997-December 1998 **Country**: Italy
Patient characteristics and setting	**Inclusion criteria**: clinically equivocal and suspicious PSLs subjected to excisional biopsy at the Institute of Dermatology **Setting**: secondary (not further specified) **Prior testing**: clinical and/or dermatoscopic suspicion **Setting for prior testing**: secondary **Exclusion criteria**: none reported **Sample size (participants):** NR **Sample size (lesions):** 256 **Participant characteristics**: none reported **Lesion characteristics**: of the CMs, 14 (25.9%) were in situ melanoma (Clark level I), 18 (33.3%) were invasive with < 0.75 mm thickness, 19 (35.3%) were of intermediate thickness (0.76-1.50 mm) and 3 (5.5%) were > 1.5 mm. The median thickness of invasive melanomas was 0.94 mm ± 0.5 (SD) (range 0.2-2.6)
Index tests	**VI**: no algorithm **Method of diagnosis:** in-person diagnosis **Prior test data**: unclear **Other test data:** clinical examination and in vivo dermoscopy were performed before excision by 2 trained dermatologists and diagnosis reached **Diagnostic threshold**: NR **Diagnosis based on**: consensus (2 observers); final clinical diagnosis was based on agreement

	between the 2 observers. In case of disagreement, the opinion of a 3rd observer (B.G.) was considered to be the judge for the diagnosis **Observer qualifications**: dermatologist **Experience in practice**: high experience or 'Expert'; described as "dermatologists with extensive experience in both clinical and dermoscopic diagnosis of pigmented skin lesions" **Dermoscopy:** evaluated in same study; pattern analysis
Target condition and reference standard(s)	**Reference standard**: histological diagnosis alone **Target condition (final diagnoses)** Melanoma (invasive): 40; melanoma (in situ): 14 BCC: 5 SK: 4; benign naevus: 90 common MN; 78 MN; 9 blue naevi; 16 Spitz reed naevi
Flow and timing	**Excluded participants**: none reported **Time interval to reference test**: NR
Comparative	In person clinical examination and dermoscopy Time interval between index test(s): the interval between the time in-vivo dermoscopy and re-evaluation of dermoscopic images was reported as 1 year
Notes	-

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Are the included patients and chosen study setting appropriate?	No		
Did the study avoid including participants with multiple lesions?	Unclear		
		Unclear	**High**
DOMAIN 2: Index Test Visual Inspection - in-person			

Carli 2002a (*Continued*)

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Unclear		
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
Was the test applied and interpreted in a clinically applicable manner?	No		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		
Was the test interpretation carried out by an experienced examiner?	Yes		
		Unclear	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		

Carli 2002a (*Continued*)

		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?			
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			
		Unclear	

Carli 2002b

Study characteristics	
Patient sampling	**Study design**: CS **Data collection**: NR **Period of data collection**: NR **Country**: Italy
Patient characteristics and setting	**Inclusion criteria**: clinically suspicious or equivocal PSLs undergoing excision for diagnostic purposes; only lesions with a diameter of $\leq$ 14 mm were included **Setting**: secondary (general dermatology) **Prior testing**: clinical suspicion of malignancy without dermatoscopic suspicion **Setting for prior testing**: secondary (general dermatology) **Exclusion criteria**: none reported **Sample size (participants)**: number included: NR **Sample size (lesions)**: number included: 57

Carli 2002b (*Continued*)

	Participant characteristics: none reported **Lesion characteristics:** thickness ≤ 1 mm: 11 cases (5 in situ 6 invasive); All ≤ 14 mm diameter
Index tests	**VI**: no algorithm **Method of diagnosis**: clinical photographs; fixed focus distance of 10 cm; images observed using a viewer in 2 separate diagnostic sessions **Prior test data**: no further information used; contact (dermoscopic) images viewed first and then distant images (clinical), without knowing the classification of the contact image of the individual lesions **Diagnostic threshold**: NR **Diagnosis based on**: consensus (2 observers); n = 2 **Observer qualifications**: dermatologist **Experience in practice**: high experience or 'Expert'; states "with experience in the field of PSL" **Other detail**: used an AF micro Nikkor 60 lens objective mounted on a NIKON f50 camera, with a fixed focus distance of 10 cm **Dermoscopy:** evaluated in same study; no algorithm
Target condition and reference standard(s)	**Reference standard**: histology (not further described) Disease positive: 21; disease negative: 36 **Target condition (final diagnoses)** Melanoma (invasive): 6; melanoma (in situ): 5; BCC: 10 'Benign' diagnoses: 36
Flow and timing	**Excluded participants**: no exclusions reported **Time interval to reference test**: photographic procedures performed consecutively prior to surgery
Comparative	Photographic procedures performed consecutively prior to surgery
Notes	-

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Are the included patients and chosen study setting appropriate?	No		

Carli 2002b (*Continued*)

Did the study avoid including participants with multiple lesions?	Unclear		
		Unclear	**High**
DOMAIN 2: Index Test Visual inspection - image-based			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Unclear		
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
Was the test applied and interpreted in a clinically applicable manner?	No		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpretation carried out by an experienced examiner?	Yes		
		Unclear	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		

Carli 2002b (*Continued*)

Expert opinion (with no histological confirmation) was not used as a reference standard	Yes		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?			
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			
		Low	

Carli 2003a

Study characteristics	
Patient sampling	**Study design**: CS **Data collection**: retrospective image selection/prospective interpretation **Period of data collection**: 1999-2001 **Country**: Italy

Carli 2003a (*Continued*)

Patient characteristics and setting	**Inclusion criteria**: clinically difficult to diagnose or equivocal melanocytic lesions randomly selected from image database; all melanomas < 1 mm thickness **Setting**: secondary (general dermatology) **Prior testing**: clinical suspicion of malignancy without dermatoscopic suspicion **Setting for prior testing**: secondary (general dermatology) **Exclusion criteria:** ≥ 1 mm thick melanomas, dermoscopically peculiar lesions (e.g. blue naevi or Spitz naevi) **Sample size (participants)**: NR **Sample size (lesions)**: number included: 200 **Participant characteristics**: none reported **Lesion characteristics**: diameter < 6 mm, 58; 6-10 mm, 87; ≥ 10 mm, 55 (results reported per subgroup) Lesions ≤ 1 mm thickness: 64; median thickness 0.3 mm, 25th-75th centile 0.00-0.58 mm; mean diameter 7.4 (SD2.79) mm; median: 7 mm (2-16 mm) **Any other detail**: same lesions appear to be reported in De Giorgi 2011 but with a different set of 8 observers (De Giorgi 2011 excluded from review on this basis)
Index tests	**VI**: no algorithm **Method of diagnosis**: clinical photographs **Prior test data**: no further information used; dermoscopic images interpreted subsequent to clinical images **Diagnostic threshold**: NR **Diagnosis based on**: average; n = 8 **Observer qualifications**: dermatology registrar; 2 final year residents. Dermatologist 6 **Experience in practice**: mixed - 2 senior experts, 4 practicing dermatologists, 2 last year resident dermatologists. Classified as 'high' due to expertise/training in dermoscopy use **Other detail**: clinical photos using Nikon F40 with macro lens at 15 cm **Dermoscopy:** evaluated in same study; no algorithm (own choice)
Target condition and reference standard(s)	**Reference standard**: histological diagnosis alone Disease positive: 64; disease negative: 136 **Target condition (final diagnoses)** Melanoma (invasive): 40; melanoma (in situ): 24 Other: 136 MN
Flow and timing	**Excluded participants**: no exclusions reported **Time interval to reference test**: interval not described
Comparative	
Notes	-

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		

Carli 2003a (*Continued*)

Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
Are the included patients and chosen study setting appropriate?	No		
Did the study avoid including participants with multiple lesions?	Unclear		
		High	**High**
DOMAIN 2: Index Test Visual inspection - image-based			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Unclear		
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
Was the test applied and interpreted in a clinically applicable manner?	No		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpretation carried out by an experienced examiner?	Yes		
		Unclear	**High**
DOMAIN 3: Reference Standard			

Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?			
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			
		Unclear	

Chang 2013

Study characteristics			
Patient sampling	**Study design**: CS **Data collection**: retrospective **Period of data collection**: January 2006-July 2009 **Country**: Taiwan		
Patient characteristics and setting	**Inclusion criteria**: potentially malignant biopsied or excised skin lesions (non-tumour specimens excluded) **Setting**: secondary (general dermatology) **Prior testing**: selected for excision (no further detail) **Setting for prior testing**: secondary (general dermatology) **Exclusion criteria:** prior surgery; image misregistered or poor-quality images (unfocused or containing a motion artefact) (considered under 'Flow and timing') **Sample size (participants)**: number eligible: 3964; number included: 676 **Sample size (lesions)**: number eligible: 4192; number included: 769 **Participant characteristics**: mean age: 47.6 (SD 21.0); male: 296; 43.8% **Lesion characteristics**: none reported		
Index tests	**VI**: no algorithm **Method of diagnosis:** in-person diagnosis **Prior test data:** N/A, in-person diagnosis **Diagnostic threshold**: NR; clinicians' impressions prior to biopsy were classified as "benign", "malignant", or "indeterminate". When the clinicians were not confident enough to make a definite benign or malignant diagnosis, the clinical impression was considered as "indeterminate". Data extracted for malignant vs rest and malignant/indeterminate vs rest **Diagnosis based on**: single observer; board-certified staff dermatologists from institute; n = 25 **Observer qualifications**: dermatologist **Experience in practice**: board certified; 'High'		
Target condition and reference standard(s)	**Reference standard**: histology (not further described) Disease positive: 174; disease negative: 595 **Target condition (final diagnoses)** Melanoma (invasive): 4; melanoma (in situ): 4; BCC: 110; cSCC: 20 'Benign' diagnoses: 595		
Flow and timing	**Excluded participants:** misregistered or poor-quality images (unfocused or containing a motion artifact) as a study inclusion criterion **Time interval to reference test**: not described		
Comparative			
Notes	-		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			

Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Are the included patients and chosen study setting appropriate?	No		
Did the study avoid including participants with multiple lesions?	No		
		Low	**High**
DOMAIN 2: Index Test Visual Inspection - in-person			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Unclear		
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
Was the test applied and interpreted in a clinically applicable manner?	Yes		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpretation carried out by an experienced examiner?	Yes		
		Unclear	**High**

Chang 2013 (*Continued*)

DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?			
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			

		High	

Collas 1999

Study characteristics	
Patient sampling	**Study design**: CS **Data collection**: prospective **Period of data collection**: January 1996 and August 1997 **Country**: France
Patient characteristics and setting	**Inclusion criteria**: PSLs undergoing excision by dermatologists in private practice, and by hospital dermatologists **Setting**: secondary (general dermatology); private care **Prior testing**: selected for excision (no further detail) **Setting for prior testing**: secondary (general dermatology); private care **Exclusion criteria**: none reported **Sample size (participants)**: number included: 353 **Sample size (lesions)**: number included: 353 **Participant characteristics**: male: 46%; 162 **Lesion characteristics**: none reported
Index tests	**VI**: no algorithm. Own new algorithm Diagnosis based on features from ABCD and 7-point checklist but neither one specifically followed Study authors selected own combination of lesion characteristics based on observed data **Method of diagnosis:** in-person diagnosis **Prior test data**: unclear **Diagnostic threshold**: data can be extracted at a number of thresholds. 1. primary diagnosis of melanoma; 2. certainty of melanoma diagnosis; 3. various combinations of assessed features (based on logistic regression) Recorded: most likely clinical diagnosis; degree of melanoma suspicion and clinical sign(s) that led to the removal decision based on ABCD rule (McCarthy 1995) and the 7-point checklist (Healsmith 1994) **Diagnosis based on**: single observer; n = NR **Observer qualifications**: dermatologist **Experience in practice**: not described **Experience with index test**: not described **Other detail**: most predictive features derived by logistic regression from the following list: irregular contours; abnormal pigmentation; blurred; frank tumor appearance; erosion, ulceration or bleeding; regression signs; lesion recently amended; lesion appeared recently; pruritic lesion; other
Target condition and reference standard(s)	**Reference standard**: histology (not further described) Disease positive: 38; disease negative: 315 **Target condition (final diagnoses)** Melanoma (in situ and invasive, or NR): 38 Other: 160

Collas 1999 (*Continued*)

Flow and timing	**Excluded participants**: no exclusions reported **Time interval to reference test**: consecutive; quote: "When the dermatologist decided to resection a pigmented lesion, he fulfilled a pre-printed sheet"		
Comparative			
Notes	-		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Are the included patients and chosen study setting appropriate?	No		
Did the study avoid including participants with multiple lesions?	Yes		
		Unclear	**High**
DOMAIN 2: Index Test Visual Inspection - in-person			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Unclear		
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?	No		

Was the test applied and interpreted in a clinically applicable manner?	Yes		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		
Was the test interpretation carried out by an experienced examiner?	Unclear		
		Unclear	**Unclear**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		

Collas 1999 (*Continued*)

If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?			
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?	Yes		
		Low	

Cristofolini 1994

Study characteristics	
Patient sampling	**Study design**: CS **Data collection**: prospective **Period of data collection**: October 1990-June 1991 **Country**: Italy
Patient characteristics and setting	**Inclusion criteria**: patients with pigmented lesions presenting during a campaign for the early diagnosis of CM at the Dermatology Department in Trento **Setting**: secondary (general dermatology) **Prior testing**: NR **Setting for prior testing**: NR **Exclusion criteria**: lesions that were not taken into consideration included benign lesions, naevi of Unna and Miescher types and naevi that showed no inclusion criteria at the ABCDE clinical examination **Sample size (participants)**: number eligible: 700 people; number included: NR **Sample size (lesions)**: number eligible: 220; number included: 220 **Participant characteristics**: none reported **Lesion characteristics**: none reported
Index tests	**VI**: ABCDE **Method of diagnosis:** in-person diagnosis **Prior test data:** N/A, in-person diagnosis **Other test data**: dermoscopy undertaken by same clinician(s) subsequent to clinical evaluation **Diagnostic threshold:** lesions showing $\geq$ 2 of the ABCDE criteria all of which were shown the same diagnostic importance, were considered positive **Diagnosis based on**: unclear; n = 4 **Observer qualifications**: dermatologist **Experience in practice**: high experience or 'Expert'; all trained in the recognition of pigmented

Cristofolini 1994 (*Continued*)

	lesions during a training course about the clinical diagnosis of naevi and melanomas; all working in a department where the early diagnosis of melanoma had been dealt with for over 10 years **Experience with dermoscopy**: high experience/'Expert' users **Other detail:** ABCDE criteria are (asymmetry in shape, border irregular and notched, colour mottled-haphazard display, dimension > 6 mm, evolution changes in pigmentation) **Dermoscopy:** evaluated in same study; pattern analysis
Target condition and reference standard(s)	**Reference standard**: histological diagnosis alone **Target condition (final diagnoses)** Melanoma (in situ and invasive, or NR): 33 Mild//moderate dysplasia: 23 dysplastic naevi; SK: 4; benign naevus: 158 common naevus Other: 2 thrombosed angiomas
Flow and timing	**Excluded participants**: no exclusions reported **Time interval to reference test**: not described **Time interval between index tests:** clinical evaluation directly followed by dermoscopy
Comparative	Clinical evaluation directly followed by dermoscopy
Notes	-

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Are the included patients and chosen study setting appropriate?	No		
Did the study avoid including participants with multiple lesions?	Unclear		
		Unclear	**High**
DOMAIN 2: Index Test Visual Inspection - in-person			

Cristofolini 1994 (*Continued*)

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
Was the test applied and interpreted in a clinically applicable manner?	Unclear		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		
Was the test interpretation carried out by an experienced examiner?	Yes		
		Low	**Unclear**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		

Cristofolini 1994 (*Continued*)

		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?			
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			
		Unclear	

Cristofolini 1997

Study characteristics	
Patient sampling	**Study design**: CS **Data collection**: prospective **Period of data collection**: November 1992-September 1993 **Country**: Italy
Patient characteristics and setting	**Inclusion criteria**: patients with small and flat common and atypical PSLs recruited during a health campaign for the early diagnosis of CM underwent clinical diagnosis, computerised analysis by SVS and subsequent skin biopsy **Setting**: secondary (general dermatology) **Prior testing**: no prior testing **Setting for prior testing**: secondary (general dermatology) **Exclusion criteria**: none reported **Sample size (participants)**: 176

	Sample size (lesions): 176 **Participant characteristics**: none reported **Lesion characteristics**: none reported
Index tests	**VI**: ABCD **Method of diagnosis:** in-person diagnosis **Prior test data**: clinical examination and/or case notes **Diagnostic threshold**: NR; examined individual ABCD characteristics but no 'rule' as to when to diagnose melanoma; appears to be subjective diagnosis **Diagnosis based on**: consensus (3 observers) (n = 3) **Observer qualifications**: dermatologist **Experience in practice**: not described in paper but judged as 'High'; states that, quote: "All lesions were examined by three dermatologists according to the ABCD system, if they disagreed a fourth dermatologist an expert in the diagnosis of pigmented lesions was consulted." Cristofolini 1994 describes 4 dermatologists "trained in the recognition of pigmented lesions", 3/4 are in common with Cristofolini 1997.
Target condition and reference standard(s)	**Reference standard**: histological diagnosis alone **Target condition (final diagnoses)** Melanoma (in situ and invasive, or NR): 35 Other: 141 MN
Flow and timing	**Excluded participants**: NR **Time interval to reference test**: quote: "subsequent skin biopsy" **Time interval between index test(s)**: NR, appears to be simultaneous
Comparative	
Notes	-

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Are the included patients and chosen study setting appropriate?	No		

Cristofolini 1997 (*Continued*)

Did the study avoid including participants with multiple lesions?	Unclear		
		Unclear	**High**
DOMAIN 2: Index Test Visual Inspection - in-person			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Unclear		
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
Was the test applied and interpreted in a clinically applicable manner?	No		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		
Was the test interpretation carried out by an experienced examiner?	Yes		
		Unclear	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		

Cristofolini 1997 (*Continued*)

Expert opinion (with no histological confirmation) was not used as a reference standard	Yes		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?			
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			
		Low	

de Giorgi 2012

Study characteristics	
Patient sampling	**Study design**: CS **Data collection**: retrospective image selection/prospective interpretation **Period of data collection**: October 2006-September 2010 **Country**: Italy

de Giorgi 2012 (*Continued*)

Patient characteristics and setting	**Inclusion criteria**: pigmented melanocytic skin lesions with a maximum diameter of 6 mm excised at Deptartment of Dermatology **Setting**: secondary (general dermatology) **Prior testing**: NR **Setting for prior testing**: NR **Exclusion criteria**: location/site of lesion - palmar and plantar regions, mucosal lesions and pigmented melanocytic lesions of the nails excluded **Sample size (participants)**: NR **Sample size (lesions)**: number included: 103 **Participant characteristics**: mean age: melanoma group male (50.4 years) female (48.4 years); benign group male (36 years) female (36.8 years) **Lesion characteristics**: head/neck: 3; trunk: 21; upper limbs/shoulder: 16; lower limbs/hip: 26; back = 34; dorsal acral = 3. Thickness**:** ≤ 1 mm 15; > 1 mm = 1 MM
Index tests	**VI**: ABCD **Method of diagnosis**: clinical photographs **Prior test data**: unclear **Other test data**: dermoscopic images also presented separately to observer (only presence/absence of particular dermoscopic features recorded; not an overall diagnostic assessment) **Diagnostic threshold:** ABCD criteria ≥ 2 criteria present **Diagnosis based on**: consensus (3 observers); n = 3 **Observer qualifications**: dermatologist **Experience in practice**: high experience or 'Expert'; quote: "the four dermatologists had the same level of training and experience in dermatology, with more than 5 years of practice in dermoscopy"
Target condition and reference standard(s)	**Reference standard**: histological diagnosis alone Disease positive: 34; disease negative: 69 **Target condition (final diagnoses)** Melanoma (in situ and invasive, or NR): 34 'Benign' diagnoses: 69 benign melanocytic nevus
Flow and timing	**Excluded participants:** none reported **Time interval to reference test**: NR
Comparative	
Notes	-

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		

Did the study avoid inappropriate exclusions?	No		
Are the included patients and chosen study setting appropriate?	No		
Did the study avoid including participants with multiple lesions?	Unclear		
		High	**High**
DOMAIN 2: Index Test Visual inspection - image-based			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	No		
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
Was the test applied and interpreted in a clinically applicable manner?	No		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		
Was the test interpretation carried out by an experienced examiner?	Yes		
		High	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		

Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?			
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			
		Unclear	

Dolianitis 2005

Study characteristics	
Patient sampling	**Study design**: CCS **Data collection**: retrospective image selection/prospective interpretation **Period of data collection**: July 2001-June 2002 **Country**: Australia
Patient characteristics and setting	**Inclusion criteria**: dermoscopy training study using a CD with 5 test sets of images, each with 40 images of melanocytic skin lesions. Only good-quality macroscopic and dermoscopic images were included **Setting**: training images; study author's institute, Deptartment of Dermatology, University of Melbourne **Prior testing:** unclear **Setting for prior testing**: NR **Exclusion criteria**: nonmelanocytic lesions; poor-quality index test image, only good-quality macroscopic and dermoscopic images were included, where the whole lesion was visible, including the entire periphery (considered under 'Flow and timing') **Sample size (participants)**: NR **Sample size (lesions)**: number eligible: 40; number included: 40 **Participant characteristics**: NR **Lesion characteristics:** $\leq$ 1 mm thickness: 14 invasive melanomas; median 0.50 mm
Index tests	**VI**: no algorithm **Method of diagnosis**: clinical photographs alone **Prior test data**: no further information used **Other test data**: dermoscopic images presented to observer subsequent to diagnosis using clinical images alone **Diagnostic threshold**: NR **Diagnosis based on**: average; 61 participants (invited to participate in a study comparing dermoscopic algorithms; advertised at several medical meetings and on a Website for primary care physicians) **Observer qualifications:** 10 dermatologists, 16 dermatology trainees, 35 GPs **Experience in practice**: mixed. Participant (volunteers), quote: "had a range of experience levels with assessment of skin lesions [outlined in detail in the paper]... and a significant number were novices in dermoscopy". Paper reports 82% of participants responded that they assessed at least 2-4 PSL per week. Participants were given explanatory written material and CDs containing educational material on dermoscopy and test images **Dermoscopy:** evaluated in same study based on dermoscopic images alone; pattern analysis; 7-point checklist; ABCD; Menzies criteria
Target condition and reference standard(s)	**Reference standard**: histological diagnosis plus other (1 lesion described as having no biopsy performed) Histology (not further described). Disease positive: 20; disease negative: 19 Expert diagnosis: 1 **Target condition (final diagnoses)** Melanoma (invasive): 18; lentigo maligna 2 Benign naevus: 7 dysplastic naevi; 3 Spitz naevi; 3 junctional naevi; 2 compound naevi; 4 other (ink-spot lentigo, blue naevus, solar lentigo, ephelis)

Flow and timing	**Excluded participants**: none reported **Time interval to reference test**: NR **Time interval between index test(s)**: NR		
Comparative			
Notes	-		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	No		
Did the study avoid inappropriate exclusions?	Unclear		
Are the included patients and chosen study setting appropriate?	No		
Did the study avoid including participants with multiple lesions?	Unclear		
		High	**High**
DOMAIN 2: Index Test Visual inspection - image-based			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Unclear		
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			

Was the test applied and interpreted in a clinically applicable manner?	No		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpretation carried out by an experienced examiner?	Unclear		
		Unclear	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Expert opinion (with no histological confirmation) was not used as a reference standard	No		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**High**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	Yes		

If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?	Unclear		
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			
		High	

Dummer 1993

Study characteristics	
Patient sampling	**Study design**: CS **Data collection**: prospective **Period of data collection**: 12-month period (year/dates NR) **Country**: Germany
Patient characteristics and setting	**Inclusion criteria**: patients with skin lesions difficult to diagnose clinically **Setting**: specialist unit (skin cancer clinic/PLC) **Prior testing**: clinical suspicion of malignancy without dermatoscopic suspicion **Setting for prior testing**: specialist unit (skin cancer clinic/PLC). A type of specialist-care-dermatology-based clinic **Exclusion criteria**: patients who had excisions performed in individual practices or where there was no histology or cases that were so obvious they did not need to have further investigation (clearly benign) **Sample size (participants)**: NR **Sample size (lesions)**: number eligible: 824; number included: 771 **Participant characteristics**: NR **Lesion characteristics**: NR
Index tests	**VI**: no algorithm **Method of diagnosis**: in person **Prior test data**: in person **Other test data**: dermoscopic images viewed separately **Diagnostic threshold:** NR **Diagnosis based on**: single observer; (n = 2 or 3) **Observer qualifications**: unclear; clinician based in dermatology clinic **Experience in practice**: unclear **Experience with index test**: unclear

Dummer 1993 (*Continued*)

Target condition and reference standard(s)	**Reference standard**: histological diagnosis alone Disease positive: 23 MM; disease negative: 748 benign **Target condition (final diagnoses)** Invasive melanoma: 23 Benign naevus 706; SK 4; benign non-melanocytic naevus 32
Flow and timing	**Excluded participants**: 53 NML not included in the final analysis (no melanomas present in this group) **Time interval to reference test**: NR **Time interval between index test(s)**: NR
Comparative	
Notes	-

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Are the included patients and chosen study setting appropriate?	No		
Did the study avoid including participants with multiple lesions?	Unclear		
		Unclear	**High**
DOMAIN 2: Index Test Visual Inspection - in-person			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Unclear		

Dummer 1993 (*Continued*)

For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
Was the test applied and interpreted in a clinically applicable manner?	Yes		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpretation carried out by an experienced examiner?	Unclear		
		Unclear	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		

Dummer 1993 (*Continued*)

Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?			
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			
		High	

Ek 2005

Study characteristics	
Patient sampling	**Study design**: CS **Data collection**: prospective **Period of data collection**: January 2001-December 2002 **Country**: Australia
Patient characteristics and setting	**Inclusion criteria**: lesions excised at tertiary referral centre for the management of cancers; only those lesions in which malignancy could not be excluded were included **Setting**: specialist unit (skin cancer clinic/PLC) **Prior testing**: selected for excision (no further detail) **Setting for prior testing**: specialist unit (skin cancer clinic/PLC) **Exclusion criteria**: punch, shave or incisional biopsies and palliative excisions. Equivocal pathology report (n = 56) **Sample size (participants)**: number eligible: 1302; number included: 1223 **Sample size (lesions)**: number eligible: 2678; number included: 2582 **Participant characteristics**: mean age: 73.6 years (16-102 years); male: 784 (64.1%); history of melanoma/skin cancer (%) 224; 8.7% recurrent lesions **Lesion characteristics**: head/neck: 61%; trunk: 14.4%; limbs: 24.6%
Index tests	**VI**: no algorithm **Method of diagnosis:** in-person diagnosis **Prior test data:** N/A, in-person diagnosis

Ek 2005 (*Continued*)

	Diagnostic threshold: NR, pre-operative diagnosis **Diagnosis based on**: unclear; likely single (n = 5) **Observer qualifications**: 3 consultants, a plastic surgery trainee and a clinical assistant **Experience in practice**: mixed (low and high experience combined); plastic surgery trainee usually 1st year, on 6-month rotation; clinical assistant described as having "many years of experience" **Other detail**: some results are presented for consultant, senior registrar and registrar but underlying patient numbers are not provided per observer to allow separate 2x2 estimation. The discussion does describe the "six MM misdiagnosed as benign … as .. assessed by non-consultants"
Target condition and reference standard(s)	**Reference standard**: histological diagnosis alone **Target condition (final diagnoses)** Melanoma (in situ and invasive, or NR): 23 BCC: 1214; cSCC: 517 'Benign' diagnoses: 188 (7.3%) SCC in situ (Bowen's disease), 330 (12.8%) solar keratoses, 63 (2.4%) seborrhoeic keratoses 247 (9.6%) were other benign lesions
Flow and timing	**Excluded participants**: lesions with incomplete or incorrectly entered proformas were excluded (n = 40) **Index to reference interval**: consecutive; used pre-operative clinical diagnosis of lesions undergoing biopsy
Comparative	
Notes	-

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
Are the included patients and chosen study setting appropriate?	Unclear		
Did the study avoid including participants with multiple lesions?	No		
		High	**High**

Ek 2005 (*Continued*)

DOMAIN 2: Index Test Visual Inspection - in-person			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Unclear		
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
Was the test applied and interpreted in a clinically applicable manner?	Yes		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpretation carried out by an experienced examiner?	Unclear		
		Unclear	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes		
Was histology interpretation carried out by an experienced histopathologist or by a der-	Unclear		

Ek 2005 (*Continued*)

matopathologist?			
		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?			
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			
		High	

Gachon 2005

Study characteristics	
Patient sampling	**Study design**: CS (dermatologists recruited and asked to use standardised questionnaire form whenever he or she decided to remove a nevus or MM for any reason, e.g. suspicion of MM, aesthetics, comfort, prevention) **Data collection**: prospective **Period of data collection**: NR **Country**: France
Patient characteristics and setting	**Inclusion criteria**: melanocytic skin lesions removed for any reason (e.g. suspicion of melanoma, aesthetics, comfort, prevention) by volunteer dermatologists **Setting**: secondary (general dermatology) and private care; mostly "community dermatologists working in a private setting, and only 2 were academic dermatologists" **Prior testing**: clinical suspicion of malignancy without dermatoscopic suspicion/patient request for

	evaluation/excision; 1199 (29.7%) excised because they were considered suspicious by the dermatologist, and 869 (21.5%) because they were considered as precursors by the dermatologist; 1634 (40.7%) removed due to aesthetic or functional reasons, and 535 (13.3%) "only to reassure the patient" **Setting for prior testing:** N/A **Exclusion criteria**: none reported **Sample size (participants)**: NR **Sample size (lesions)**: number included: 4036 **Participant characteristics**: none reported **Lesion characteristics:** 36 (24.1%) of 149 melanoma were in situ or other invasive lesions with a median Breslow thickness of 0.60 mm
Index tests	**VI**: no algorithm. Accuracy presented only for clinician's first clinical impression of lesions; after recording likelihood of melanoma, assessments were made as to the contributions of pattern recognition, ABCD criteria and ugly duckling (differential recognition) **Method of diagnosis:** in-person diagnosis **Prior test data:** N/A, in-person diagnosis **Diagnostic threshold:** 'considered suspicious' by dermatologist **Diagnosis based on**: single observer; (n = 135 of 200 volunteers) **Observer qualifications**: dermatologist **Experience in practice**: not described; most were community dermatologists working in a private setting, and 2 were academic dermatologists **Experience with index test**: not described
Target condition and reference standard(s)	**Reference standard**: histological diagnosis alone Disease positive: 149; disease negative: 3887 **Target condition (final diagnoses)** Melanoma (in situ and invasive, or NR): 149 (36 were in situ or other invasive lesions with a median Breslow thickness of 0.60 mm) 'Benign' diagnoses: 3629 naevi (89.9%); 4 uncertain MMs/naevi (0.1%); and 254 NML clinically considered to be naevi or MMs (6.3%)
Flow and timing	**Excluded participants**: none reported **Time interval to reference test**: NR
Comparative	
Notes	-

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		

Gachon 2005 (*Continued*)

Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Are the included patients and chosen study setting appropriate?	No		
Did the study avoid including participants with multiple lesions?	Unclear		
		Unclear	**High**
DOMAIN 2: Index Test Visual Inspection - in-person			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Unclear		
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
Was the test applied and interpreted in a clinically applicable manner?	Yes		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpretation carried out by an experienced examiner?	Unclear		
		Unclear	**High**
DOMAIN 3: Reference Standard			

Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?			
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			
		Unclear	

Green 1991

Study characteristics			
Patient sampling	**Study design**: CS **Data collection**: prospective **Period of data collection**: February 1989-August 1990 **Country**: Australia		
Patient characteristics and setting	**Inclusion criteria**: pigmented lesions with complete clinical and histological data **Setting**: secondary (referred from surgery, dermatology, casualty) **Prior testing**: NR **Setting for prior testing**: surgery, dermatology and casualty departments **Exclusion criteria**: none reported **Sample size (participants)**: number eligible: 81/number included: unclear **Sample size (lesions)**: number eligible: 89; number included: 70 **Participant characteristics**: median age 32 years; male 36 (44%) **Lesion characteristics:** site trunk: 80%; limbs: 10%; face and neck 10%		
Index tests	**VI**: no algorithm **Method of diagnosis:** in-person **Prior test data:** in-person **Diagnostic threshold**: NR, clinical diagnosis recorded plus assessment of diameter, colour, regularity of outline, diffuseness of edge and palpability **Diagnosis based on**: single observer; (n = NR) **Observer qualifications**: mixed; "in the majority of cases a surgeon or a dermatologist" **Experience in practice**: not described		
Target condition and reference standard(s)	Reference standard**;** histological diagnosis and expert diagnosis Histology: 62/70 lesions Expert diagnosis: 8/70 lesions; 8 lesions had clinical diagnoses assigned (all benign) in the absence of available histology reports **Target condition (final diagnoses)** Melanoma (in situ and invasive, or NR): 5 BCC: 2; SK: 7; benign naevus: 53 oOther: 2 skin tags, 1 'lentigo'		
Flow and timing	**Excluded participants:** 19/89 lesions excluded due to incomplete clinical and histology records **Time interval to reference test**: assumed consecutive; pathology referral form used to ascertain clinical diagnosis		
Comparative			
Notes	-		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			

Green 1991 (*Continued*)

Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Are the included patients and chosen study setting appropriate?	No		
Did the study avoid including participants with multiple lesions?	Unclear		
		Unclear	**High**
DOMAIN 2: Index Test Visual Inspection - in-person			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Unclear		
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
Was the test applied and interpreted in a clinically applicable manner?	Yes		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpretation carried out by an experienced examiner?	Unclear		
		Unclear	**High**

Green 1991 (*Continued*)

DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	No		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Expert opinion (with no histological confirmation) was not used as a reference standard	No		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		High	**High**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	No		
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?			
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			

		High	

Green 1994

Study characteristics	
Patient sampling	**Study design**: CS **Data collection**: NR; appears to use previously acquired images to develop a new CAD classifier (not included as derivation), and compare results to clinical diagnosis of clinicians as recorded in notes. Unclear whether set up prospectively or was retrospective assessment **Period of data collection**: August 1990-April 1992 **Country**: Australia
Patient characteristics and setting	**Inclusion criteria**: pigmented lesions for excision **Setting**: secondary (Deptartment of Surgery) **Prior testing**: selected for excision (no further detail) **Setting for prior testing**: NR **Exclusion criteria**: none reported **Sample size (participants)**: number included: 129 **Sample size (lesions)**: number eligible: 204; number included: 164 **Participant characteristics**: mean age 36 years, range 6-87 years; male: 42.6% **Lesion characteristics:** site face/neck: 10%, trunk: 66%, limbs: 24%
Index tests	**VI**: no algorithm **Method of diagnosis:** in-person diagnosis **Prior test data**: no further information used **Diagnostic threshold**: NR; clinical diagnosis recorded plus assessment of diameter, colour, regularity of outline, diffuseness of edge and palpability (same as for Green 1991) **Diagnosis based on**: single observer; (n = NR) **Observer qualifications**: NR **Experience in practice**: not described
Target condition and reference standard(s)	**Reference standard**: histology (not further described) Disease positive: 18; disease negative: 146 **Target condition (final diagnoses)** Melanoma (invasive): 18; melanoma (in situ): 3 128 MN; 15 miscellaneous pigmented lesions including seborrhoeic keratoses, BCCs, and lentigines
Flow and timing	**Excluded participants**: 33 lesions excluded due to problems using the images with the CAD software, e.g. lesion "too big"; image "obscured by hairs or surgeons pen marks" or "software was unable to contend with the lesion characteristics, mainly because the lesion was too light or too fragmented" or "avoidable operator error" **Time interval to reference test**: NR
Comparative	
Notes	-

Green 1994 (*Continued*)

Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Are the included patients and chosen study setting appropriate?	No		
Did the study avoid including participants with multiple lesions?	No		
		Unclear	**High**
DOMAIN 2: Index Test Visual Inspection - in-person			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Unclear		
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
Was the test applied and interpreted in a clinically applicable manner?	Yes		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		

Green 1994 (*Continued*)

Was the test interpretation carried out by an experienced examiner?	Unclear		
		Unclear	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?			

Green 1994 (*Continued*)

If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			
		High	

Grimaldi 2009

Study characteristics	
Patient sampling	**Study design**: CS **Data collection**: prospective **Period of data collection**: October 2005-March 2006 **Country**: Italy
Patient characteristics and setting	**Inclusion criteria**: cutaneous pigmented lesions with digital images forwarded by primary care physicians to a referral centre for confirmation of diagnosis **Setting**: primary; lesions selected for referral by GPs; accuracy of GP diagnosis assessed **Prior testing**: NR **Setting for prior testing**: NR **Exclusion criteria**: lesions whose removal had been explicitly demanded by the patients for aesthetic reasons, as well as those irritated or subjected to trauma **Sample size (participants)**: number included: 197 **Sample size (lesions)**: number included: 235 **Participant characteristics**: none reported **Lesion characteristics**: none reported
Index tests	**VI**: no algorithm **Method of diagnosis:** in-person diagnosis **Prior test data:** N/A, in-person diagnosis **Other test data:** "two-step judgment (before and after dermoscopy) formulated by the sending physician, who labelled each lesion as 'benign' or 'suspicious for malignancy'." **Diagnostic threshold**: NR, quote, "Each physician was asked to formulate a written first judgment of every lesion before digital acquisition and to re-evaluate it after dermoscopy" **Diagnosis based on**: single observer; (n = 13) **Observer qualifications:** GP; from approximately 250 primary care clinicians attending a conference, 13 volunteered to participate **Experience in practice**: not clearly described; assumed to be low experience with pigmented lesions **Experience in dermoscopy**: unclear; classified as 'trained', "simple protocols for diagnosis were made up and given to the participants via e-learning courses, direct meetings, and involving self assessment procedures" **Dermoscopy:** evaluated in same study; no algorithm (ABCD used for telediagnosis at reference centre)

Target condition and reference standard(s)	**Reference standard**: histological diagnosis plus follow-up (reference is expert diagnosis for teledermatology component of study) Histology (not further described): n = 16;*d*isease positive: 5; disease negative: 11 Clinical follow-up (6 months) plus histology of suspicious lesions: n = 219; disease positive: 0; disease negative: 208 **Target condition (final diagnoses)** Melanoma (in situ and invasive, or NR): 5 Other: 230 benign		
Flow and timing	**Excluded participants**: NR **Time interval to reference test**: NR **Time interval between index test(s)**: NR		
Comparative			
Notes	-		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Are the included patients and chosen study setting appropriate?	Yes		
Did the study avoid including participants with multiple lesions?	No		
		Low	**High**
DOMAIN 2: Index Test Visual Inspection - in-person			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		

If a threshold was used, was it pre-specified?	Unclear		
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
Was the test applied and interpreted in a clinically applicable manner?	Yes		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpretation carried out by an experienced examiner?	No		
		Unclear	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	No		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		High	**Unclear**
DOMAIN 4: Flow and Timing			

Grimaldi 2009 (*Continued*)

Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	Yes		
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?	Yes		
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			
		High	

Kopf 1975

Study characteristics	
Patient sampling	**Study design**: CS **Data collection**: retrospective **Period of data collection**: 1955-1967 **Country**: USA
Patient characteristics and setting	**Inclusion criteria**: all lesions subject to biopsy at the Oncology Section of the Skin and Cancer Unit **Setting**: specialist unit (skin cancer clinic/PLC) **Prior testing**: NR **Setting for prior testing**: NR **Exclusion criteria**: none reported **Sample size (participants)**: number included: NR **Sample size (lesions)**: number included: 5538 **Participant characteristics**: none reported **Lesion characteristics**: none reported

Kopf 1975 (*Continued*)

Index tests	**VI**: no algorithm **Method of diagnosis:** in-person diagnosis **Prior test data**: unclear **Diagnostic threshold**: NR; clinical diagnosis **Diagnosis based on**: single observer; in-clinic diagnosis (n = NR) **Observer qualifications:** oncologist **Experience in practice**: not described **Experience with index test**: not described
Target condition and reference standard(s)	**Reference standard**: histological diagnosis alone Disease positive: 99; disease negative: 5439 **Target condition (final diagnoses)** Melanoma (invasive): 99 (described as "malignant melanoma") Diagnoses listed only for false-positives; included: 3 pigmented BCC, 3 DFs, 2 junction naevi, 2 compound naevi, and 1 each of: Kaposi sarcoma, hemangioma, SK, leiomyoma, cellular blue nevus, sclerosing hemangioma, SCC, verrucous nevus, and intradermal nevus FNs included: 6 clinically diagnosed as pigmented BCC; 2 "other forms" of BCC; 3 junction naevi; 3 pyogenic granulomas; 2 compound naevi; 2 SCCs; 2 halo naevi; 1 Bowen disease; 1 SK; and 1 lentigo. 17 of these lesions were pigmented and 6 were not
Flow and timing	**Excluded participants**: none reported **Time interval to reference test**: NR
Comparative	
Notes	-

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Are the included patients and chosen study setting appropriate?	No		
Did the study avoid including participants with multiple lesions?	Unclear		

Kopf 1975 (*Continued*)

		Low	**High**
DOMAIN 2: Index Test Visual Inspection - in-person			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Unclear		
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
Was the test applied and interpreted in a clinically applicable manner?	Yes		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpretation carried out by an experienced examiner?	Unclear		
		Unclear	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes		

Kopf 1975 (*Continued*)

Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?			
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			
		Unclear	

Krahn 1998

Study characteristics	
Patient sampling	**Study design**: CS **Data collection**: prospective **Period of data collection**: NR **Country**: Germany
Patient characteristics and setting	**Inclusion criteria**: excised PSLs **Setting**: secondary (general dermatology) **Prior testing**: NR

Krahn 1998 (*Continued*)

	Setting for prior testing: NR **Exclusion criteria**: none reported **Sample size (participants)**: number included: 80 **Sample size (lesions)**: number included: 80 **Participant characteristics**: none reported **Lesion characteristics** range in thickness (melanomas) 0.18-1.9 mm; 29/39 < 0.76 mm; 7/39 0.76-1.5 mm; 3/39 > 1.5 mm
Index tests	**VI**: no algorithm reported **Method of diagnosis:** in-person diagnosis **Prior test data**: unclear **Other test data**: dermoscopy undertaken by same clinician(s) subsequent to clinical evaluation **Diagnostic threshold**: NR; no details **Diagnosis based on**: single observer (n = 1) **Observer qualifications**: NR, likely dermatologist **Experience in practice**: not described **Experience with index test**: not described **Dermoscopy:** evaluated in same study; no algorithm
Target condition and reference standard(s)	**Reference standard**: histological diagnosis alone including histometrics Disease positive: 39; disease negative: 41 **Target condition (final diagnoses)** Melanoma (invasive): 39 (SSM, lentigo MM, nodular M) Benign naevus: 37 common n**a**evus; 3 dysplastic nevus, 1 Spitz naevus
Flow and timing	**Excluded participants**: none reported **Time interval to reference test:** NR **Time interval between index test(s)**: NR
Comparative	
Notes	-

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		

Are the included patients and chosen study setting appropriate?	No		
Did the study avoid including participants with multiple lesions?	Yes		
		Unclear	**High**
DOMAIN 2: Index Test Visual Inspection - in-person			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Unclear		
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
Was the test applied and interpreted in a clinically applicable manner?	Yes		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpretation carried out by an experienced examiner?	Unclear		
		Unclear	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		

Krahn 1998 (*Continued*)

Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?			
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			
		Unclear	

Langley 2001

Study characteristics	
Patient sampling	**Study design**: CS **Data collection**: prospective **Period of data collection**: NR **Country**: USA
Patient characteristics and setting	**Inclusion criteria**: patients with lesions scheduled for excision at the PLC to either remove atypical naevi or to rule out melanoma or for cosmetic reasons **Setting**: specialist unit (skin cancer clinic/PLC) **Prior testing**: selected for excision; to remove atypical naevi or rule out melanoma or for cosmetic reasons **Setting for prior testing**: NR **Exclusion criteria**: none reported **Sample size (participants)**: number included: 29 **Sample size (lesions)**: number eligible: 40; number included: 38 **Participant characteristics**: mean age 39 years, range 19-95 years; male: 14 (48%) **Lesion characteristics**: none reported
Index tests	**VI**: no algorithm **Method of diagnosis:** in-person diagnosis **Prior test data:** N/A, in-person diagnosis **Diagnostic threshold**: NR; clinical diagnosis **Diagnosis based on**: unclear likely in clinic diagnoses (n = NR) **Observer qualifications**: NR, likely dermatologists **Experience in practice**: not described **Experience with index test**: not described
Target condition and reference standard(s)	**Reference standard**: histological diagnosis plus other Histology details (n = 38): "After excision, the samples were processed in paraffin and stained with H&E for routine light microscopy. Correlation was performed by examining the confocal images and the pathology sections to compare nuclear, cellular, and morphologic detail and to identify potential significance of the in vivo CSLM observations. For the histologic diagnosis of dysplastic naevi, we used the criteria that are defined in the World Health Organization consensus study." Expert diagnosis (n = 2): 2 lesions did not undergo histology; expert diagnosis only (both benign) **Target condition (final diagnoses)** Melanoma (invasive): 3; melanoma (in situ): 1; lentigo maligna 2 Dysplastic naevi: 17; benign naevus: 15
Flow and timing	**Excluded participants**: none reported **Time interval to reference test**: NR **Time interval between index test(s)**: NR
Comparative	
Notes	-
Methodological quality	

Langley 2001 (*Continued*)

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Are the included patients and chosen study setting appropriate?	Unclear		
Did the study avoid including participants with multiple lesions?	No		
		Unclear	**High**
DOMAIN 2: Index Test Visual Inspection - in-person			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Unclear		
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
Was the test applied and interpreted in a clinically applicable manner?	Unclear		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		

Was the test interpretation carried out by an experienced examiner?	Unclear		
		Unclear	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Expert opinion (with no histological confirmation) was not used as a reference standard	No		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**High**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?			

If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			
		Unclear	

Lorentzen 1999

Study characteristics	
Patient sampling	**Study design**: CS **Data collection**: prospective **Period of data collection**: 1994-1997 **Country**: Denmark
Patient characteristics and setting	**Inclusion criteria**: patients with lesions suspicious for CMM referred to outpatients clinic **Excluded participants**: none reported **Time interval to reference test**: NR **Setting**: NR **Prior testing**: clinical suspicion of malignancy without dermatoscopic suspicion **Setting for prior testing**: NR **Exclusion criteria**: poor-quality index test image (considered under flow/timing) **Sample size (participants)**: number eligible: 242; number included: 232 **Sample size (lesions)**: number eligible: 242; number included: 232* **Participant characteristics**: none reported **Lesion characteristics**: none reported *NB Not all cases were assessed by all observers; 2x2 are based on presented sensitivity and specificity estimates for full dataset of lesions; "the dermatoscopy experts assessed almost all cases (98 ± 100%) , whereas the non-expert group completed fewer assessments, from 76 to 98%."
Index tests	**VI**: no algorithm **Method of diagnosis**: clinical photographs **Prior test data**: no further information used; no option to change clinical diagnosis after viewing dermoscopic image **Other test data**: dermoscopic images presented to observer subsequent to diagnosis using clinical images alone; clinical images presented before dermoscopic images **Diagnostic threshold**: NR; clinical diagnosis **Diagnosis based on**: average; n = 9 **Observer qualifications**: dermatologist **Experience in practice**: high; moderate; mixed (average reported); 4 "experienced dermatologists" (4-5 years daily experience) and 5 "non-expert dermatology residents" (1-2 years' interest and formal training in dermatoscopy) **Experience with index test**: high; moderate; mixed

Target condition and reference standard(s)	**Reference standard**: histological diagnosis alone Disease positive: 65 ; disease negative: 167 **Target condition (final diagnoses)** Melanoma (invasive): 49 "malignant melanoma" BCC: 16 SK: 12; benign naevus: 137 (pigmented naevi = 116; blue naevi = 16; atypical naevi = 5); Other: 18 (Spitz naevi, Bowen's disease, sarcoid, nevus spilus, hemangioma, and others)		
Flow and timing	**Excluded participants**: 10 cases were "considered unfit for evaluation" due to poor-quality image **Reference interval**: "biopsy specimens...were obtained after the clinical and dermatoscopic photographs had been performed"		
Comparative			
Notes	-		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Are the included patients and chosen study setting appropriate?	No		
Did the study avoid including participants with multiple lesions?	Unclear		
		Unclear	**High**
DOMAIN 2: Index Test Visual inspection - image-based			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		

If a threshold was used, was it pre-specified?	Unclear		
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
Was the test applied and interpreted in a clinically applicable manner?	No		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpretation carried out by an experienced examiner?	Yes		
		Unclear	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**Unclear**
DOMAIN 4: Flow and Timing			

Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?			
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			
		High	

McGovern 1992

Study characteristics	
Patient sampling	**Study design**: CS **Data collection**: prospective **Period of data collection**: 1 November 1989-31 October 1990 **Country**: USA
Patient characteristics and setting	**Inclusion criteria**: pigmented lesions excised to rule out dysplasia, lentigo maligna or MM **Setting**: secondary (general dermatology); army dermatology clinic - appears to be open access **Prior testing**: no prior testing. Multiple reasons given for seeking dermatological consultation, including (in descending order): increasing size, "mole check", inflammation, colour change, itch, follow-up, variegation, cosmetic, referral, irregular border, seen for other lesion, unknown, large size **Setting for prior testing**: N/A **Exclusion criteria**: none reported **Sample size (participants)**: number eligible: 179; number included: NR **Sample size (lesions)**: number eligible: 237; number included: 13 lesions excluded and 32 lesions unaccounted for **Participant characteristics**: mean age: 44 (SD 18); range: 3 months to 86 years; male: 89 (49%) **Lesion characteristics:** lesion site: head/neck: 71 (30%); trunk: 52 (23%); upper limbs/shoulder:

	22 (9%); lower limbs/hip: 33 (14%); back = 58 (24%); genitalia = 1 (0.4%)
Index tests	**VI**: ABCD; assessed only 'BCD'; also referred to in paper as 3-point checklist; Glasgow/MacKie original 7-point checklist (Keefe 1990) **Method of diagnosis:** in-person diagnosis **Prior test data**: unclear **Diagnostic threshold**: described in detail; ABCD excluded asymmetry - one half does not match the other half) **Diagnosis based on**: single observer in clinic diagnoses used (n = NR) **Observer qualifications**: NR, likely dermatologists **Experience in practice**: not described Any other details: border irregularity, edges are ragged, notched, or blurred; colour irregularity, pigmentation is not uniform, shades of tan, brown and black are present with dashes of red, white, or blue; diameter > 6 mm, the size of a pencil eraser 7-point: increasing size, variegation, inflammation, irregular outline, > 1 cm diameter, itch, bleeding, **1** point awarded for each feature
Target condition and reference standard(s)	**Reference standard**: histological diagnosis alone Details: shave excision = 109; punch biopsy = 64; excision = 47; snip biopsy = 17 Disease positive: 16 lesions; disease negative: 221 **Target condition (final diagnoses)** Melanoma (invasive): 6; lentigo maligna 6; BCC: 4; Dysplastic naevus 28; SK: 32; benign naevus: 110; lentigo 12; blue naevus 9; AK 6; DF 6; atypical naevus 4; other 14
Flow and timing	**Excluded participants**: missing data for the different algorithms; approximately 32 lesions unaccounted for (13 excluded due to lesion size of ≤ 8 mm). ABCD evaluated = 192/224 lesions; 3-point evaluated = 192/224 lesions; 7-point evaluated = 205/224 lesions **Time interval to reference test**: NR
Comparative	
Notes	-

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		

Are the included patients and chosen study setting appropriate?	Unclear		
Did the study avoid including participants with multiple lesions?	No		
		Low	**High**
DOMAIN 2: Index Test Visual Inspection - in-person			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	No		
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?	Unclear		
Was the test applied and interpreted in a clinically applicable manner?	Yes		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		
Was the test interpretation carried out by an experienced examiner?	Unclear		
		High	**Unclear**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		

McGovern 1992 (*Continued*)

Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?			
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?	Unclear		
		High	

Menzies 2009

Study characteristics	
Patient sampling	**Study design**: CS **Data collection**: prospective **Period of data collection**: December 2005-August 2006 **Country**: Australia
Patient characteristics and setting	**Inclusion criteria**: pigmented lesions which, after routine naked eye examination by the GP, would have been biopsied or referred, i.e. a suspicious pigmented lesion. GPs were recruited from practices with at least 3 clinicians; excluded if they already used dermoscopy or SDDI in their routine practice **Setting**: primary **Prior testing**: clinical suspicion of malignancy without dermatoscopic suspicion **Setting for prior testing**: primary **Exclusion criteria**: none reported **Sample size (participants):** NR **Sample size (lesions)**: number included: 374 **Participant characteristics**: none reported **Lesion characteristics**: none reported
Index tests	**VI**: no algorithm **Method of diagnosis:** in-person diagnosis **Prior test data**: N/A in-person diagnosis **Other test data:** clinical diagnosis and placed in a sealed envelope before proceeding to dermoscopy examination **Diagnostic threshold**: NR; initial diagnosis recorded along with confidence of diagnosis (scale 1-10; 1 not at all confident and 10 extremely confident), certainty of melanoma (scale 0%-100%; 0 definitely not melanoma and 100 definitely melanoma) and management (biopsy, referral) **Diagnosis based on**: single observer (n = 63; 102 GPs initially recruited; 74 (72.5%) completed the educational intervention and online assessment; 63 GPs from 19 practices finally participated) **Observer qualifications:** GP **Experience in practice**: not fully described; assumed to be low experience with pigmented lesions. GPs must have each excised or referred $\geq$ 10 PSL in previous 12-month period; excluded if dermoscopy or SDDI already used in routine practice. During the pretrial period all GPs underwent a training programme in the use of dermoscopy **Dermoscopy:** evaluated in same study; no algorithm
Target condition and reference standard(s)	**Reference standard**: histological diagnosis plus other Histology (not further described): described as to standard practice and not necessarily blinded to the GP's diagnosis; author confirmed that all melanoma had histological diagnosis and > 50% of benign had histology or follow-up Total excised or referred: 163. Immediate excision/referral: 110. Excision/referral after SDDI: 48. Excision/examination after patient self-referral 5 Disease positive: 37; disease negative: total of 126 benign or unknown were 'excised OR referred' so some would have had specialist diagnosis only Clinical follow-up plus histology of suspicious lesions: short-term digital monitoring (SDDI) available as an option for lesions considered not to be melanoma but that were still considered suspicious; follow-up imaging occurred initially at 3 months with any morphological changes to result in biopsy or referral; some lesions continued SDDI for a further 3 months; length of follow-up: 3-6 months Number of participants: initially recommended for SDDI: 192; SDDI continued for further 3

	months: 6; Underwent SDDI only (no excision): 146 Disease positive: 15 (SDDI then histologically confirmed); disease negative: 176 benign (including 1 missed in situ melanoma); 4 unknown Expert opinion: GPs could refer for specialist opinion or lesions could undergo dermoscopy telemedicine (images reviewed by an expert in dermoscopy and SDDI). Dermoscopy telemedicine was blinded to the GP's diagnosis. Observe for change group, i.e. discharged after dermoscopy: 72, plus a proportion of those in excise/refer group will have had expert diagnosis alone but details not given Disease positive: 0; disease negative: 71 benign; 1 unknown **Target condition (final diagnoses)** Melanoma (invasive): 33; melanoma (in situ): 1 BCC: 6 2 Bowen's disease; 323 benign; 9 unknown		
Flow and timing	**Excluded participants**: 9 lesions with unknown diagnoses, plus BCC and Bowen's excluded from some analyses **Time interval to reference test**: NR; histopathological and specialist examination occurred according to standard practice		
Comparative			
Notes	-		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Are the included patients and chosen study setting appropriate?	Yes		
Did the study avoid including participants with multiple lesions?	Unclear		
		Low	**Unclear**
DOMAIN 2: Index Test Visual Inspection - in-person			

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Unclear		
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
Was the test applied and interpreted in a clinically applicable manner?	Yes		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpretation carried out by an experienced examiner?	No		
		Unclear	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	No		
Were the reference standard results interpreted without knowledge of the results of the index tests?	No		
Expert opinion (with no histological confirmation) was not used as a reference standard	No		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		

		High	**High**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	No		
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?	Yes		
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			
		High	

Morales Callaghan 2008

Study characteristics	
Patient sampling	**Study design**: CS **Data collection**: prospective **Period of data collection**: 1 January 2005-31 December 2005 **Country**: Spain
Patient characteristics and setting	**Inclusion criteria**: randomly selected melanocytic lesions; melanocytic on both clinical and dermoscopic criteria **Setting**: secondary (general dermatology) **Prior testing**: dermatoscopic suspicion in all cases **Setting for prior testing**: NR **Exclusion criteria**: location/site of lesion, palms, soles, mucous membranes of face, under nails; non-melanocytic appearance **Sample size (participants)**: number included: 166

	Sample size (lesions): number included: 200 **Participant characteristics**: mean age 33.7 years (SD 14.5), range 8-84 years; male: 64 (38.6%); Fitzpatrick phototype II (44%); type III (41.5%) **Lesion characteristics**: macular component = 181 (90.5%), papular component = 125 (62.5%), both = 106 (53%), either one or other = 94 (47%). Asymmetrical 144 (72%). Irregular borders 154 (77%). 4 colours in 40 (20%), 3 colours in 96 (48%), 2 colours in 57 (28.5%), 1 colour in 1 (0.5%). History of bleeding 7 (3.5%). Changes reported by participant 154 (77%). Lesion site: trunk 155 (77.5%), including the back in 106 (53%). Lesion size: mean long axis diameter 7.9 mm (SD 8.6) mm, mean short axis diameter 5.1 (SD 5)		
Index tests	**VI**: no algorithm **Method of diagnosis:** in-person diagnosis **Prior test data**: clinical examination and/or case notes **Other test data**: appears that dermoscopy was undertaken by same clinician(s) subsequent to clinical evaluation; clinical history was constructed following a standardised protocol and a presumptive clinical diagnosis recorded. Each lesion was then photographed and immediately afterwards examined using a manual dermatoscope **Diagnostic threshold**: NR; presumptive clinical diagnosis **Diagnosis based on**: consensus (n = 2) **Observer qualifications**: dermatologist **Experience in practice**: not clearly described; assumed to be high - "both dermatologists had experience in dermoscopy." **Dermoscopy:** evaluated in same study; pattern analysis		
Target condition and reference standard(s)	**Reference standard**: histological diagnosis alone Details: lesions described using terminology proposed by US National Institutes of Health Disease positive: 6/6 lesions; disease negative: 194/194 lesions (assuming the 9 'other' diagnosis lesions were not malignant), or 185/185 (removing the 9 'other' diagnosis lesions from dataset) **Target condition (final diagnoses)** Melanoma (in situ and invasive, or NR): 6 (3%) Other: atypical mole = 104, common mole = 70, congenital naevus = 6, blue nevus = 3, Spitz/Reed naevus = 1, spilus naevus = 1, others (unclear whether benign or malignant) = 9		
Flow and timing	**Exclusions**: none reported **Time interval to reference test**: "Samples for histologic analysis were taken immediately after clinical and dermoscopic examination" **Time interval between index test(s)**: images taken at same time		
Comparative			
Notes	-		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			

Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
Are the included patients and chosen study setting appropriate?	No		
Did the study avoid including participants with multiple lesions?	No		
		High	**High**
DOMAIN 2: Index Test Visual Inspection - in-person			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Unclear		
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
Was the test applied and interpreted in a clinically applicable manner?	No		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpretation carried out by an experienced examiner?	Yes		
		Unclear	**High**

DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?			
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			

		Low	

Morton 1998a

Study characteristics	
Patient sampling	**Study design**: CS **Data collection**: retrospective **Period of data collection**: 1992-1994 **Country**: Scotland
Patient characteristics and setting	**Inclusion criteria**: all biopsies generated at PLC during time period **Setting**: specialist unit (skin cancer clinic/PLC) **Prior testing**: NR **Setting for prior testing:** N/A **Exclusion criteria**: none reported **Sample size (participants)**: number eligible: 1999 **Sample size (lesions):** 763 lesions examined by 1 of 2 consultants **Participant characteristics**: none reported **Lesion characteristics**: none reported
Index tests	**VI**: no algorithm **Method of diagnosis:** in-person diagnosis **Prior test data:** N/A, in-person diagnosis referred to as "clinical diagnosis"; no dermoscopy used **Diagnostic threshold**: NR; clinical diagnosis **Diagnosis based on**: single observer and average data presented; (n = 10 in total) **Observer qualifications:** 2 consultant dermatologists **Experience in practice**: high (2 consultants each with > 10 years' experience in dermatology) **Any other detail**: data from same study for senior registrar and registrar presented in Morton 1998b and Morton 1998c
Target condition and reference standard(s)	**Reference standard**: histological diagnosis alone **Target condition (final diagnoses; for full sample of 1999 biopsies)** Melanoma (invasive): 102 (82 SSM, 11 nodular melanoma, 4 partially regressed, 2 acral lentiginous, 2 metastatic CM deposits, 1 desmoplastic melanoma); melanoma (in situ): 24; lentigo maligna: 2 Benign: 1871 benign (breakdown by lesion type NR)
Flow and timing	**Excluded participants**: none reported **Time interval to reference test**: NR **Time interval between index test(s)**: N/A
Comparative	
Notes	-

Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**

Morton 1998a (*Continued*)

DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Are the included patients and chosen study setting appropriate?	No		
Did the study avoid including participants with multiple lesions?	Unclear		
		Unclear	**High**
DOMAIN 2: Index Test Visual Inspection - in-person			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Unclear		
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
Was the test applied and interpreted in a clinically applicable manner?	Yes		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpretation carried out by an experienced examiner?	Yes		

Morton 1998a (*Continued*)

		Unclear	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?			
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms			

Morton 1998a (*Continued*)

1 month or less?			
		Unclear	

Morton 1998b

Study characteristics	
Patient sampling	**Study design**: CS **Data collection**: retrospective **Period of data collection**: 1992-1994 **Country**: Scotland
Patient characteristics and setting	**Inclusion criteria**: all biopsies generated at PLC during time period **Setting**: specialist unit (skin cancer clinic/PLC) **Prior testing**: NR **Setting for prior testing:** N/A **Exclusion criteria**: none reported **Sample size (participants)**: number eligible: 1999 **Sample size (lesions):** 567 lesions examined by senior registrar **Participant characteristics**: NR **Lesion characteristics**: NR
Index tests	**VI**: no algorithm **Method of diagnosis:** in-person diagnosis **Prior test data:** N/A, in-person diagnosis referred to as 'clinical diagnosis'; no dermoscopy used **Diagnostic threshold**: NR; clinical diagnosis **Diagnosis based on**: single observer and average data presented; (n = 10 in total) **Observer qualifications:** 2 senior registrars **Experience in practice**: moderate, 2 senior registrars each with 3-5 years' experience **Any other detail**: data from same study for consultants and for registrar presented in Morton 1998a and Morton 1998c
Target condition and reference standard(s)	**Reference standard**: histological diagnosis alone **Target condition (final diagnoses; for full sample of 1999 biopsies)** Melanoma (invasive): 102 (82 SSM, 11 nodular melanoma, 4 partially regressed, 2 acral lentiginous, 2 metastatic CM deposits, 1 desmoplastic melanoma); melanoma (in situ): 24; lentigo maligna: 2 Benign: 1871 benign (breakdown by lesion type NR)
Flow and timing	**Excluded participants**: none reported **Time interval to reference test**: NR **Time interval between index test(s)**: N/A
Comparative	
Notes	The study by Morton et al is considered as a single study for quality assessment purposes (as per Morton 1998a) but as three studies (Morton 1998a; Morton 1998b; Morton 1998c) for the analyses due to the reporting of three separate cohorts of participants

Morton 1998b (*Continued*)

Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Are the included patients and chosen study setting appropriate?			
Did the study avoid including participants with multiple lesions?			
DOMAIN 2: Index Test Visual Inspection - in-person			
Were the index test results interpreted without knowledge of the results of the reference standard?			
If a threshold was used, was it pre-specified?			
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
Was the test applied and interpreted in a clinically applicable manner?			
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?			

Was the test interpretation carried out by an experienced examiner?			
DOMAIN 2: Index Test Visual inspection - image-based			
Were the index test results interpreted without knowledge of the results of the reference standard?			
If a threshold was used, was it pre-specified?			
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
Was the test applied and interpreted in a clinically applicable manner?			
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?			
Was the test interpretation carried out by an experienced examiner?			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?			
Were the reference standard results interpreted without knowledge of the results of the index tests?			

Morton 1998b (*Continued*)

Expert opinion (with no histological confirmation) was not used as a reference standard			
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?			
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?			
Did all patients receive the same reference standard?			
Were all patients included in the analysis?			
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?			
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			

Morton 1998c

Study characteristics	
Patient sampling	**Study design**: CS **Data collection**: retrospective **Period of data collection**: 1992-1994 **Country**: Scotland

Patient characteristics and setting	**Inclusion criteria**: all biopsies generated at PLC during time period **Setting**: specialist unit (skin cancer clinic/PLC) **Prior testing**: NR **Setting for prior testing:** N/A **Exclusion criteria**: NR **Sample size (participants)**: number eligible: 1999 **Sample size (lesions):** 669 lesions examined by registrar **Participant characteristics**: NR **Lesion characteristics**: NR
Index tests	**VI**: no algorithm **Method of diagnosis:** in-person diagnosis **Prior test data:** N/A, in-person diagnosis referred to as 'clinical diagnosis'; no dermoscopy used **Diagnostic threshold:** NR; clinical diagnosis **Diagnosis based on**: single observer and average data presented; (n = 10 in total) **Observer qualifications**: registrars **Experience in practice**: low, 6 rotating registrars each with 1-2 years' experience **Any other detail**: data from same study for consultants and for senior registrars presented in Morton 1998a and Morton 1998b
Target condition and reference standard(s)	**Reference standard**: histological diagnosis alone **Target condition (final diagnoses; for full sample of 1999 biopsies)** Melanoma (invasive): 102 (82 SSM, 11 nodular melanoma, 4 partially regressed, 2 acral lentiginous, 2 metastatic CM deposits, 1 desmoplastic melanoma); melanoma (in situ): 24; lentigo maligna: 2 Benign: 1871 benign (breakdown by lesion type NR)
Flow and timing	**Excluded participants**: none reported **Time interval to reference test**: NR **Time interval between index test(s)**: N/A
Comparative	
Notes	The study by Morton et al is considered as a single study for quality assessment purposes (as per Morton 1998a) but as three studies (Morton 1998a; Morton 1998b; Morton 1998c) for the analyses due to the reporting of three separate cohorts of participants

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		

Did the study avoid inappropriate exclusions?	Unclear		
Are the included patients and chosen study setting appropriate?			
Did the study avoid including participants with multiple lesions?			
DOMAIN 2: Index Test Visual Inspection - in-person			
Were the index test results interpreted without knowledge of the results of the reference standard?			
If a threshold was used, was it pre-specified?			
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
Was the test applied and interpreted in a clinically applicable manner?			
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?			
Was the test interpretation carried out by an experienced examiner?			
DOMAIN 2: Index Test Visual inspection - image-based			
Were the index test results interpreted without knowledge of the results of the reference stan-			

Morton 1998c (*Continued*)

dard?			
If a threshold was used, was it pre-specified?			
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
Was the test applied and interpreted in a clinically applicable manner?			
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?			
Was the test interpretation carried out by an experienced examiner?			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?			
Were the reference standard results interpreted without knowledge of the results of the index tests?			
Expert opinion (with no histological confirmation) was not used as a reference standard			
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?			
DOMAIN 4: Flow and Timing			

Morton 1998c (*Continued*)

Was there an appropriate interval between index test and reference standard?			
Did all patients receive the same reference standard?			
Were all patients included in the analysis?			
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?			
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			

Pizzichetta 2004

Study characteristics	
Patient sampling	**Study design**: CS **Data collection**: retrospective image selection/prospective interpretation **Period of data collection**: January 1996-December 2001 **Country**: participants recruited from 5 participating centres (4 in Italy and 1 in USA) study conducted in Italy
Patient characteristics and setting	**Inclusion criteria**: clinical and/or dermoscopic hypomelanotic (extent of pigmentation $\leq$ 30%) and amelanotic skin lesions seen and excised at the 5 participating centres **Setting**: secondary (general dermatology) **Prior testing**: clinical and/or dermatoscopic suspicion **Setting for prior testing**: NR **Exclusion criteria**: poor-quality or unavailable index test image (considered under 'Flow and timing') **Sample size (participants)**: number included: 151 **Sample size (lesions)**: number eligible: 174; number included: 151 **Participant characteristics:** mean age 47 years (± 17.5 SD); male: 73 (48%) **Lesion characteristics**: lesion site, head/neck (5.3%); trunk (20.5%); upper limbs/shoulder (11.9%)

	; lower limbs/hip (25.2%); back (21.2%); abdomen (11.3%); hand (3.3%); foot (1.3%). Melanoma thickness: ≤ 1 mm 85.3% (n = 29); > 1 mm 14.7% (n = 15)
Index tests	**VI**: no algorithm **Method of diagnosis**: clinical photographs **Prior test data:** only the gender, age at diagnosis and the site of the skin lesion were known to the observer **Other test data**: file contained clinical and dermoscopic images; unclear whether both observed at the same time **Diagnostic threshold:** investigated clinical features such as elevation, ulceration, shape, borders, colour **Diagnosis based on**: single observer (n = 1) **Observer qualifications**: NR, likely dermatologist **Experience in practice**: not described **Experience with index test**: not described **Dermoscopy:** evaluated in same study; pattern analysis
Target condition and reference standard(s)	**Reference standard**: histological diagnosis alone **Target condition (final diagnoses)** Melanoma (invasive): 34 (39 in full sample); melanoma (in situ): 5 Other diagnoses reported only for full sample of 151 (only 108 with clinical images for VI evaluation) : 55 (40 with clinical images) "amelanotic hypomelanotic non melanocytic lesions" (25 BCC, 4 SCC, 10 DF, 8 Bowen's disease, 8 SK) 52 (29 with clinical images) "amelanotic hypomelanotic benign melanocytic lesions" (24 compound naevi, 17 dermal naevi, 5 Spitz naevi, 4 congenital naevi and 2 combined naevi)
Flow and timing	**Excluded participants:** 23 lesions excluded due to image quality; further 43 lesions were not available for evaluation by clinical images ("mainly benign melanocytic lesions") **Time interval to reference test**: NR **Time interval between index test(s):** NR
Comparative	
Notes	-

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Unclear		

Did the study avoid inappropriate exclusions?	Yes		
Are the included patients and chosen study setting appropriate?	No		
Did the study avoid including participants with multiple lesions?	Yes		
		Unclear	**High**
DOMAIN 2: Index Test Visual inspection - image-based			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Unclear		
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
Was the test applied and interpreted in a clinically applicable manner?	No		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpretation carried out by an experienced examiner?	Unclear		
		Unclear	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		

Pizzichetta 2004 (*Continued*)

Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?			
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			
		High	

Rao 1997

Study characteristics	
Patient sampling	**Study design**: CS **Data collection**: retrospective image selection/prospective interpretation **Period of data collection**: NR **Country**: USA
Patient characteristics and setting	**Inclusion criteria**: patients with atypical melanocytic lesions or suspected early MM **Setting**: private care **Prior testing**: selected for excision (no further detail) **Setting for prior testing**: private care **Exclusion criteria:** lesions > 13 mm in diameter were excluded as they could not fit entirely within the standardised photographs **Sample size (participants)**: number included: 63 **Sample size (lesions)**: number included: 72 **Participant characteristics**: none reported **Lesion characteristics**: melanoma thickness ≤ 1 mm: 100% of MM (n = 21)
Index tests	**VI** ABCD **Method of diagnosis**: clinical photographs **Prior test data**: unclear **Other test data**: dermoscopic images also presented to observer but unclear whether both viewed at the same time or not; "Each color transparency was independently analyzed" by observers. The 1) clinical, 2) "overall" dermoscopic, and 3) ABCD "scored dermoscopic diagnoses" of either MM or AMN were recorded for each lesion by the same observers. No indication of blinding between images **Diagnostic threshold**: clinical variables were defined as follows: asymmetry (A): both silhouette and colour distribution were considered. Border irregularity (B): this was judged by the unevenness of the perimeter. Colour (C): colour variegation and number of colours were evaluated. Diameter (D): the largest in situ diameter in mm of each lesion was recorded **Diagnosis based on**: single observer (n = 4) **Observer qualifications**: 2 experienced dermatologists, and 2 melanoma fellows **Experience in practice**: mixed experience (low and high experience combined) **Experience with index test**: NR **Dermoscopy:** evaluated in same study; ABCD and no algorithm
Target condition and reference standard(s)	**Reference standard**: histological diagnosis alone Details: each of the 72 melanocytic neoplasms was histopathologically diagnosed as with AMN or an early MM by a dermapathologist with special expertise in melanocytic neoplasms. Each lesion was completely excised and step-sectioned. Disease positive: 21 MMs; disease negative: 51 AMN **Target condition (final diagnoses)** Melanoma (invasive): 21 51 AMN
Flow and timing	**Excluded participants**: none reported **Time interval to reference test**: NR **Time interval between index test(s)**: NR

Comparative			
Notes	-		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Are the included patients and chosen study setting appropriate?	No		
Did the study avoid including participants with multiple lesions?	No		
		Unclear	**High**
DOMAIN 2: Index Test Visual inspection - image-based			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Unclear		
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
Was the test applied and interpreted in a clinically applicable manner?	No		

Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpretation carried out by an experienced examiner?	Yes		
		Unclear	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application			

Rao 1997 (*Continued*)

of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?			
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			
		Low	

Rosendahl 2011

Study characteristics	
Patient sampling	**Study design**: CS **Data collection**: retrospective image selection/prospective interpretation **Period of data collection**: 30-month period; dates NR **Country**: Australia
Patient characteristics and setting	**Inclusion criteria**: consecutive series of pigmented lesions submitted for histology from the primary care skin cancer practice of one study author **Setting**: primary care skin cancer practice **Prior testing**: selected for excision (no further detail) **Setting for prior testing**: primary **Exclusion criteria**: poor image quality (considered under 'Flow and timing'); no other exclusion criteria reported **Sample size (participants)**: number included: 389 **Sample size (lesions)**: number eligible: 466 pigmented lesions out of 1959 lesions excised or biopsied; number included: 463 **Participant characteristics**: mean age: 57 years (SD 17); male: 67.4% **Lesion characteristics:** (53.1%) melanocytic. Lesion site: 17.7% head or face; trunk: 52.1%; 27.6% extremities; 2.2% palms or soles. Melanoma thickness: ≤ 1 mm: 1/29 melanoma (3.4%)
Index tests	**VI**: no algorithm **Method of diagnosis**: clinical photographs overview and close-up image presented **Prior test data**: no further information used **Other test data**: dermoscopic images presented to observer subsequent to diagnosis using clinical images alone **Diagnostic threshold**: clinical diagnosis/subjective impression. Observers gave a diagnosis with level of confidence (from 0 for definitely benign to 100 for definitely malignant) after viewing the clinical images. (NB used study authors' threshold for detection of any skin cancer that includes lesions clinically considered to be MM, BCC pigmented epithelial carcinoma including SCC, keratoacanthoma, AK and Bowen's disease as test-positive; review only considered histologically confirmed MM, BCC or invasive SCC to be disease-positive) **Diagnosis based on**: single observer (n = NR) **Observer qualifications**: expert dermatologist (based on author communication) **Experience in practice**: expert

	Experience with dermoscopy: expert		
Target condition and reference standard(s)	**Reference standard**: histological diagnosis alone Details: excise or biopsy Disease positive: 138; disease negative: 325 **Target condition (final diagnoses)** Melanoma (invasive): 9; melanoma (in situ): 20; BCC: 72; cSCC: 5 (including 2 keratoacanthoma) 'Benign' diagnoses*: 18 Bowen's disease and 14 AK, 217 benign melanocytic plus additional 140 benign non melanocytic *authors considered Bowen's disease, AK and keratoacanthoma as malignant; all considered benign for review analysis		
Flow and timing	**Excluded participants**: lesions were excluded due to poor image quality (n = 3) **Time interval to reference test**: unclear; lesions "routinely photographed" if scheduled for excision or biopsy but not further described **Time interval between index test(s)**: consecutive		
Comparative			
Notes	-		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Are the included patients and chosen study setting appropriate?	Yes		
Did the study avoid including participants with multiple lesions?	No		
		Low	**High**
DOMAIN 2: Index Test Visual inspection - image-based			

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Unclear		
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
Was the test applied and interpreted in a clinically applicable manner?	No		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpretation carried out by an experienced examiner?	Yes		
		Unclear	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		

Rosendahl 2011 (*Continued*)

		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?			
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			
		High	

Scope 2008

Study characteristics	
Patient sampling	**Study design**: CS **Data collection**: retrospective image selection/prospective interpretation **Period of data collection**: after January 2003 **Country**: NR
Patient characteristics and setting	**Inclusion criteria**: images of PSLs selected from a database of standardised patient images provided by a New Zealand-based teledermatology company (MoleMap). Images were selected on the basis that (1) at least 8 clinically atypical naevi were apparent on the back; (2) most of the lesions on the back and all of the atypical naevi had close-up clinical digital images; (3) 1-year follow-up images (close-up clinical and dermoscopic images) were available to show that lesions considered to be benign were in fact biologically indolent by revealing no change; and (4) the image quality of both the overview and the close-up images were acceptable **Setting:** New Zealand-based teledermatology company; images were sent electronically to partici-

	pants as a PowerPoint file **Prior testing**: NR **Setting for prior testing**: unspecified **Exclusion criteria**: poor-quality index test image (considered under 'Flow and timing'); naevi on any body site except the back **Sample size (participants)**: number eligible: 12; number included: 12 **Sample size (lesions)**: number eligible: 145; number included: 145 **Participant characteristics**: none reported **Lesion characteristics**: none reported
Index tests	**VI**: ugly duckling **Method of diagnosis**: clinical photographs **Prior test data**: no further information used **Diagnostic threshold**: for each lesion that was deemed as different, the participants had to mark the lesion number on the form, identify it as either completely different or somewhat different from the other moles, give a short qualitative description of how the lesion differed, and report whether they would like to have a biopsy performed on the lesion **Diagnosis based on**: average (n = 34) **Observer qualifications**: 4 subgroups in terms of clinical expertise: group 1, pigmented lesion experts (n = 8); group 2, dermatologists who were considered non-experts in pigmented lesion evaluation (n = 13); group 3, dermatology nurses (n = 5, including 1 dermatology medical photographer) ; and group 4, non-clinical medical staff (n = 8) **Experience in practice**: mixed experience (low and high experience combined) **Other detail**: the study was sent electronically to participants as a PowerPoint file (Microsoft Corp, Redmond, Washington) that contained the clinical image interface and a Word document that contained questionnaire and response forms. The participants were not shown dermoscopic images. However, dermoscopic images of lesions (with a 1-year follow-up dermoscopic image) were available to the investigators to verify that lesions considered benign did not show dermoscopic features suggestive of malignancy, and the 1-year follow-up images confirmed that the lesions were in fact biologically indolent by revealing no change
Target condition and reference standard(s)	Reference standard: histological diagnosis plus follow-up **Details**: unclear; all MMs were excised with histological confirmation and all benign had 1-year follow-up images (close-up clinical and dermoscopic images) to show that lesions considered to be benign were in fact biologically indolent by revealing no change, not clear whether any of the benign group were excised **Target condition (final diagnoses)** Melanoma (invasive): 5 "malignant melanoma" Benign naevus: 140
Flow and timing	**Excluded participants:** excluded if unacceptable image quality of both the overview and the close-up images **Time interval to reference test:** NR
Comparative	
Notes	-
Methodological quality	

Scope 2008 (*Continued*)

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Are the included patients and chosen study setting appropriate?	Unclear		
Did the study avoid including participants with multiple lesions?	No		
		Unclear	**High**
DOMAIN 2: Index Test Visual inspection - image-based			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	No		
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
Was the test applied and interpreted in a clinically applicable manner?	No		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		

Was the test interpretation carried out by an experienced examiner?	Yes		
		High	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Expert opinion (with no histological confirmation) was not used as a reference standard	Unclear		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	No		
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?	Yes		

If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			
		High	

Soyer 1995

Study characteristics	
Patient sampling	**Study design**: CS **Data collection**: unclear **Period of data collection**: NR **Country**: Austria
Patient characteristics and setting	**Inclusion criteria**: PSL, difficult to diagnose on clinical grounds alone **Setting**: specialist unit (skin cancer clinic/PLC) **Prior testing**: clinical suspicion **Setting for prior testing**: secondary (general dermatology); referred by dermatologists or general physicians **Exclusion criteria**: none reported **Sample size (participants):** NR **Sample size (lesions)**: number included: 159 **Participant characteristics**: none reported **Lesion characteristics** "23 melanomas with a Breslow index of ≤ 0.75 mm, 13 melanomas with a Breslow index ≥ 0.76 mm and ≤ 1.5 mm, 12 melanomas with a Breslow index ≥ 1.51 mm and ≤ 3.5 mm, 2 melanomas with a Breslow index of ≥ 3.5 mm."
Index tests	**VI**: no algorithm **Method of diagnosis:** in-person diagnosis **Prior test data:** N/A in-person diagnosis **Other test data**: dermoscopy undertaken by same clinician(s) subsequent to clinical evaluation **Diagnostic threshold**: NR **Diagnosis based on:** n = 2 (1 or 2 per lesion) **Observer qualifications**: dermatologist **Experience in practice**: not clearly described; assumed to be high; "Each lesion was examined clinically by .. one of the authors .. and a clinical diagnosis was recorded." "After application of a drop of immersion oil, each lesion was examined dermoscopically …; the examination was performed by a dermatologist expert in dermoscopy and a dermoscopic diagnosis was recorded" **Experience with index test**: not described **Other detail:** "Photographic documentation was performed using an incident light stereomicroscope (Wild M 650) equipped with a Minolta XG-M camera" **Dermoscopy:** evaluated in same study; pattern analysis

Soyer 1995 (*Continued*)

Target condition and reference standard(s)	**Reference standard**: histological diagnosis alone Disease positive: 65 (41%); disease negative: 94 (59%) **Target condition (final diagnoses)** Melanoma (invasive): 50; melanoma (in situ): 15 BCC: pigmented BCC (3) SK: 18; Clark's naevus of dysplastic naevus (61 cases); lentigo actinica lentigo (2), pigmented AK (4), angioma (3), angiokeratoma (2)		
Flow and timing	**Excluded participants**: none reported **Time interval to reference test**: NR		
Comparative			
Notes	-		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Are the included patients and chosen study setting appropriate?	Unclear		
Did the study avoid including participants with multiple lesions?	Unclear		
		Unclear	**Unclear**
DOMAIN 2: Index Test Visual Inspection - in-person			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Unclear		

Soyer 1995 (*Continued*)

For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
Was the test applied and interpreted in a clinically applicable manner?	Yes		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpretation carried out by an experienced examiner?	Yes		
		Unclear	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		

Soyer 1995 (*Continued*)

Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?			
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			
		Unclear	

Stanganelli 1998a

Study characteristics	
Patient sampling	**Study design**: CCS **Data collection**: retrospective image selection/prospective interpretation **Period of data collection**: just states 1997 **Country**: Italy
Patient characteristics and setting	**Inclusion criteria**: images of PSLs selected from computerised files of the skin cancer clinic **Setting**: training study; images selected from skin cancer clinic **Prior testing**: NR **Setting for prior testing**: unspecified **Exclusion criteria**: none reported **Sample size (participants)**: NR **Sample size (lesions)**: number included: 30 PSLs **Participant characteristics**: none reported **Lesion characteristics**: none reported
Index tests	**VI**: no algorithm **Method of diagnosis**: clinical photographs **Prior test data**: no further information used **Other test data**: dermascopic images presented to observer subsequent to diagnosis using clinical images alone (images were randomised) **Diagnostic threshold**: NR

Stanganelli 1998a (*Continued*)

	Diagnosis based on: average; n = 20 **Observer qualifications**: dermatologist **Experience in practice**: not described; 30 dermatologists with "experience in ELM but [with] no formal training" attended a seminar on clinical and ELM diagnosis of PSL; 20 then participated in a test of their diagnostic accuracy. A second session on ELM was then held **Other detail**: the observers received 2-h seminar of the principles of clinical diagnosis of NMLs, BCC, MN and MM. The participants were then invited to undergo an anonymous test of their diagnostic accuracy **Dermoscopy:** evaluated in same study; no algorithm		
Target condition and reference standard(s)	**Reference standard**: histological diagnosis alone **Target condition (final diagnoses)** Melanoma (in situ and invasive, or NR): 10 BCC: 4 Mild/moderate dysplasia: 3; SK: 3; benign naevus: MN-7 Other: 1 hemangioma, 1 subungunal haemorrhage, 1 plantar intraepidermal haemorrhage		
Flow and timing	**Excluded participants**: none reported **Time interval to reference test**: NR		
Comparative			
Notes	-		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	No		
Did the study avoid inappropriate exclusions?	Unclear		
Are the included patients and chosen study setting appropriate?	No		
Did the study avoid including participants with multiple lesions?	Unclear		
		High	**High**

Stanganelli 1998a (*Continued*)

DOMAIN 2: Index Test Visual inspection - image-based			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Unclear		
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
Was the test applied and interpreted in a clinically applicable manner?	No		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpretation carried out by an experienced examiner?	Unclear		
		Unclear	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes		
Was histology interpretation carried out by an experienced histopathologist or by a der-	Unclear		

Stanganelli 1998a (*Continued*)

matopathologist?			
		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?			
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			
		Unclear	

Stanganelli 2000

Study characteristics	
Patient sampling	**Study design**: CS **Data collection**: retrospective **Period of data collection**: 1994-1996 **Country**: Italy
Patient characteristics and setting	**Inclusion criteria**: patients with PSLs referred by dermatologists and general practitioners either for pre-surgical assessment or consultation **Setting**: specialist unit (skin cancer clinic/PLC) **Prior testing:** patients referred for pre-surgical assessment or consultation indicating they have had prior tests **Setting for prior testing**: primary, some patients referred for consultation only; dermoscopy findings reported back and management decision remains with referring clinician; secondary (general

Stanganelli 2000 (*Continued*)

	dermatology) **Exclusion criteria**: none reported **Sample size (participants)**: number eligible: 1556 **Sample size (lesions)**: number eligible: 3372; number included: 3372 **Participant characteristics**: median age 30 years, range 10-94; male: 522 (34%) **Lesion characteristics**: none reported
Index tests	**VI**: ABCD **Method of diagnosis:** in-person diagnosis **Prior test data:** N/A, in-person diagnosis **Other test data**: dermoscopic and clinical images subsequently presented separately to observer subsequent to diagnosis using clinical images alone **Diagnostic threshold**: NR **Diagnosis based on**: single observer; n = 1 **Observer qualifications**: NR; described as one of the co-authors and study based in skin cancer clinic; likely dermatologist **Experience in practice**: not described **Other detail**: a crude clinical image (magn x6 and x10) was recorded in the digital database **Dermoscopy:** evaluated in same study (image-based); pattern analysis
Target condition and reference standard(s)	**Reference standard**: histological diagnosis plus follow-up; histology report of known surgical excisions (n = 262) plus a cancer registry-based follow-up of benign cases (n = 3110) **Target condition (final diagnoses)** Melanoma (in situ and invasive, or NR): 55; BCC: 43 'Benign' diagnoses: 3274
Flow and timing	**Excluded participants**: none reported **Time interval to reference test**: NR **Time interval between index test(s)**: not clearly reported just indicated that D-ELM was performed soon after clinical examination
Comparative	
Notes	-

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		

Are the included patients and chosen study setting appropriate?	Yes		
Did the study avoid including participants with multiple lesions?	No		
		Low	**High**
DOMAIN 2: Index Test Visual Inspection - in-person			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
Was the test applied and interpreted in a clinically applicable manner?	Yes		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		
Was the test interpretation carried out by an experienced examiner?	Unclear		
		Low	**Unclear**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	No		
Were the reference standard results	Unclear		

interpreted without knowledge of the results of the index tests?			
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		High	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	Yes		
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?	Yes		
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			
		High	

Stanganelli 2005

Study characteristics	
Patient sampling	**Study design**: unclear (likely CS) **Data collection**: retrospective image selection/prospective interpretation **Period of data collection**: NR **Country**: Italy **Test set derived:** a training set of 22 melanomas and 218 MN was randomised from the dataset. The test set was formed by the complement (the remaining 20 melanomas and 217 naevi). A further subset of images from the original dataset, consisting of 31 melanomas and 103 naevi, was used for the comparison between observers and CAD; derivation of the subset NR
Patient characteristics and setting	**Inclusion criteria**: melanocytic lesions from patients referred to the Skin Cancer Unit and undergoing clinical and dermoscopic evaluation; images were 'selected' from a larger image database. Potential overlap with Stanganelli 2000 (not possible to determine). **Setting**: specialist unit (skin cancer clinic/PLC) **Prior testing**: clinical and/or dermatoscopic suspicion **Setting for prior testing**: specialist unit (skin cancer clinic/PLC) **Exclusion criteria**: none reported **Sample size (participants)**: number eligible: 1556. Referred/number included: NR **Sample size (lesions)**: number eligible: 3274. Number included: 477 melanocytic lesions; 237 in test set and 134 in comparison between CAD and human operators **Participant characteristics**: none reported **Lesion characteristics**: melanoma thickness 61.2% < 0.75 mm
Index tests	**VI**: no algorithm **Method of diagnosis**: clinical photographs **Prior test data**: GPs evaluated only clinical images; unclear for dermatologists **Other test data**: dermatologists examined both clinical and dermoscopic images but unclear whether clinical diagnosis was made prior to presentation of dermoscopic images **Diagnostic threshold**: NR **Diagnosis based on**: average (n = 6) **Observer qualifications:** GP 3; dermatologist 3 **Experience in practice**: assumed low for GPs; high for dermatologists. Described as "dermatologists with experience in ELM (2 years)" **Other detail**: digital images included melanocytic lesions evaluated in ELM with a fixed x16 magnification **Dermoscopy:** evaluated in same study; no algorithm
Target condition and reference standard(s)	**Reference standard**: histological diagnosis plus cancer registry All included lesions underwent histology but some were identified using a cancer registry-based follow-up of benign diagnoses **Target condition (final diagnoses)** Melanoma (in situ and invasive, or NR): 42 in full sample; 31 in CAD vs human observer interp and 20 in test set 'Benign' diagnoses: 435 MN; 103 in CAD-observer comp and 217 in test set
Flow and timing	**Excluded participants**: none reported **Time interval to reference test**: NR

Comparative			
Notes	-		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Unclear		
Did the study avoid inappropriate exclusions?	Unclear		
Are the included patients and chosen study setting appropriate?	No		
Did the study avoid including participants with multiple lesions?	Unclear		
		Unclear	**High**
DOMAIN 2: Index Test Visual inspection - image-based			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Unclear		
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
Was the test applied and interpreted in a clinically applicable manner?	No		

Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpretation carried out by an experienced examiner?	Yes		
		Unclear	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Expert opinion (with no histological confirmation) was not used as a reference standard	Unclear		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	Yes		
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application			

of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?			
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			
		High	

Steiner 1987

Study characteristics	
Patient sampling	**Study design**: CS **Data collection**: prospective **Period of data collection**: not specified **Country**: Austria
Patient characteristics and setting	**Inclusion criteria**: small (< 10 mm) PSLs considered diagnostically equivocal in that there was no absolute agreement on the clinical diagnosis among investigating clinicians at a PLC **Setting**: specialist unit (skin cancer clinic/PLC) **Prior testing**: clinical suspicion of malignancy without dermatoscopic suspicion **Setting for prior testing**: specialist unit (skin cancer clinic/PLC) **Exclusion criteria**: none reported **Sample size (participants):** NR **Sample size (lesions):** 318 **Participant characteristics**: none reported **Lesion characteristics**: none reported
Index tests	**VI**: no algorithm **Method of diagnosis:** in-person diagnosis **Prior test data:** N/A **Other test data**: dermoscopy undertaken by same clinician(s) subsequent to clinical evaluation **Diagnostic threshold**: NR **Diagnosis based on**: consensus (3 observers) "All lesions were independently seen and diagnosed by the three investigators, and the diagnosis that appeared most probable to at least two of the three investigators was recorded as the clinical"; n = 3 **Observer qualifications**: dermatologist **Experience in practice**: high experience or 'Expert' "experienced dermatologists" **Experience with index test:** "experienced dermatologists"
Target condition and reference standard(s)	**Reference standard**: histological diagnosis alone Disease positive: 73 melanomas, 20 BCCs; disease negative: 225 **Target condition (final diagnoses)** Melanoma (invasive): 49; melanoma (in situ): 15; lentigo maligna 9 (also includes lentigo maligna melanoma)

Steiner 1987 (*Continued*)

	BCC: 20 SK: 20; junctional naevi 39; blue naevus 29; dysplastic naevus 75; LS and nevoid lentigo 19; angioma/angiokeratoma 15		
Flow and timing	**Excluded participants**: none reported **Time interval to reference test**: assumed consecutive; following diagnosis, lesions subsequently excised **Time interval between index test(s)**: consecutive		
Comparative			
Notes	-		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Are the included patients and chosen study setting appropriate?	No		
Did the study avoid including participants with multiple lesions?	Unclear		
		Unclear	**High**
DOMAIN 2: Index Test Visual Inspection - in-person			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Unclear		

For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
Was the test applied and interpreted in a clinically applicable manner?	No		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpretation carried out by an experienced examiner?	Yes		
		Unclear	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		

Steiner 1987 (*Continued*)

Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?			
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			
		Low	

Thomas 1998

Study characteristics	
Patient sampling	**Study design**: CCS; separate recruitment **Data collection**: retrospective **Period of data collection**: NR; appears to be post-1992 **Country**: France
Patient characteristics and setting	**Inclusion criteria**: retrospective selection of all 460 cases of melanoma and a nonselected consecutive group of 680 nonmelanoma pigmented tumours **Setting**: secondary (general dermatology) **Prior testing**: selected for excision (no further detail). All excised **Setting for prior testing**: NR **Exclusion criteria**: NR **Sample size (participants)**: NR **Sample size (lesions)**: number included: 1140 **Participant characteristics**: NR **Lesion characteristics: Other test data**: dermoscopy undertaken by same clinician(s) subsequent to clinical evaluation
Index tests	**VI**: ABCDE **Method of diagnosis:** in-person diagnosis; dermatologist making referral for excision made the diagnosis **Prior test data:** N/A in-person diagnosis

Thomas 1998 (*Continued*)

	Diagnostic threshold: number of characteristics present (from ≥ 1 to all 5) **Diagnosis based on**: single observer; n = NR **Observer qualifications**: dermatologist **Experience in practice**: assumed to be high; described as 'trained' dermatologists **Other detail**: preliminary meeting held to precisely define each criterion, agree on the significance of each abnormality and define the appropriate way to fill in the study form. ABCDE: criterion A was defined as geometrical asymmetry in two axes of the tumour, criterion B as irregular (unsharp or ill-defined or angular) borders, criterion C as presence of at least 2 different colours within the lesion (with the exception of the usual symmetrical darkening of the lesion in its centre), criterion D as diameter ≥ 6 mm. Criterion E, the only anamnestic (based on the patient's description of the natural history of the lesion) criterion was defined as enlargement of the surface (and not in height) of the lesion
Target condition and reference standard(s)	**Reference standard**: histological diagnosis alone Disease positive: 460; disease negative: 680 **Target condition (final diagnoses)** Melanoma (in situ and invasive, or NR): 460 BCC: 8 SK: 19; 576 benign pigmented naevus; 55 dysplastic naevi; 4 blue naevi; 2 compound naevi with Sutton inflammatory infiltrate; 2 Spitz; 1 Reed's naevi; 3 haemangiomas; 9 DFs; 1 accessory nipple
Flow and timing	**Excluded participants**: none reported **Time interval to reference test**: NR
Comparative	
Notes	-

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	No		
Did the study avoid inappropriate exclusions?	Unclear		
Are the included patients and chosen study setting appropriate?	No		
Did the study avoid including participants with multiple lesions?	Unclear		

Thomas 1998 (*Continued*)

		High	**High**
DOMAIN 2: Index Test Visual Inspection - in-person			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	No		
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
Was the test applied and interpreted in a clinically applicable manner?	Yes		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		
Was the test interpretation carried out by an experienced examiner?	Yes		
		High	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	No		
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes		

Thomas 1998 (*Continued*)

Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?			
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			
		Unclear	

Troyanova 2003

Study characteristics	
Patient sampling	**Study design**: CCS **Data collection**: retrospective image selection/prospective interpretation **Period of data collection**: NR **Country**: NR
Patient characteristics and setting	**Inclusion criteria**: Images of PSLs $\leq$ 13 mm in diameter selected for a dermoscopy training study **Setting**: training study **Prior testing**: NR

	Setting for prior testing: NR **Exclusion criteria**: NR **Sample size (participants)**: NR **Sample size (lesions)**: number included: 50 lesions **Participant characteristics**: NR **Lesion characteristics**: melanoma thickness: ≤ 1 mm: 100%
Index tests	**VI**: no algorithm **Method of diagnosis**: clinical photographs and dermoscopic images **Other test data**: dermoscopic images presented to observer subsequent to diagnosis using clinical images alone **Prior test data**: no further information used **Diagnostic threshold**: NR **Diagnosis based on**: average; n = 32 **Observer qualifications**: dermatologist **Experience in practice**: high experience or 'Expert' **Experience with index test**: low experience/novice users; experienced in PSL field but not ELM **Dermoscopy:** evaluated in same study; no algorithm
Target condition and reference standard(s)	**Reference standard**: histological diagnosis alone Disease positive: 25; disease negative: 25 **Target condition (final diagnoses)** Melanoma (in situ and invasive, or NR): 25 'Benign' diagnoses: 25 "not melanoma"
Flow and timing	**Excluded participants**: none reported **Time interval to reference test**: NR **Time interval between index test(s)**: NR
Comparative	
Notes	-

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	No		
Did the study avoid inappropriate exclusions?	Unclear		

Are the included patients and chosen study setting appropriate?	No		
Did the study avoid including participants with multiple lesions?	Unclear		
		High	**High**
DOMAIN 2: Index Test Visual inspection - image-based			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Unclear		
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
Was the test applied and interpreted in a clinically applicable manner?	No		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpretation carried out by an experienced examiner?	Yes		
		Unclear	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		

Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?			
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			
		Unclear	

Unlu 2014

Study characteristics	
Patient sampling	**Study design**: CS **Data collection**: retrospective image selection/prospective interpretation **Period of data collection**: January 2008-January 2010 **Country**: Turkey
Patient characteristics and setting	**Inclusion criteria**: melanocytic lesions excised at Ankara University Department of Dermatology PLC **Setting**: specialist unit (skin cancer clinic/PLC) Ankara University Department of Dermatology PLC **Prior testing**: selected for excision (no further detail) **Setting for prior testing**: specialist unit (skin cancer/PLC) **Exclusion criteria**: location/site of lesion facial, nail and volar acral lesions were excluded; non-melanocytic appearance **Sample size (participants)**: number included: 115 **Sample size (lesions)**: number included: 115 **Participant characteristics**: mean age: 38.72 years (+/- 18.46 years); male: n = 56 (49%) **Lesion characteristics**: lesion site: 100% trunk and limbs. Melanoma thickness: 10 (41.7%) < 0.75 mm; 14 (58.3%) ≥ 0.75 mm
Index tests	**VI**: no algorithm; appears to be original clinical diagnosis at time of lesion presentation **Method of diagnosis:** in-person diagnosis. Appears to be diagnosis on presentation **Prior test data:** N/A, in-person diagnosis **Other test data**: dermoscopic images presented to different observers **Diagnostic threshold**: NR **Diagnosis based on**: unclear. For VI appears to be single examiner at time of clinic diagnosis (n = NR); dermoscopic images "scored by three other experienced dermatoscopists" (n = 3) **Observer qualifications**: NR; assumed dermatologists. Described as experienced dermatoscopists **Experience in practice**: unclear for clinic diagnosis; dermatoscopists described as "experienced" **Experience with index test**: described as "experienced" **Dermoscopy:** evaluated in same study by 3 experienced dermoscopists; 3-point rule; 7-point checklist; ABCD; CASH algorithm (image-based)
Target condition and reference standard(s)	**Reference standard**: histological diagnosis alone Disease positive: 24; disease negative: 91 **Target condition (final diagnoses)** Melanoma (in situ and invasive, or NR): 24 'Benign' diagnoses: 91 melanocytic benign lesions; 37 (32.2%) dermal naevi; 15 (13%) Clark's naevi; 14 (12.2%) compound naevi; 13 (11.3%) blue naevi; 6 (5.2%) Spitz naevi; 4 (3.5%) congenital MN; 2 (1.7%) junctional naevi
Flow and timing	**Excluded participants**: none reported **Time interval to reference test**: NR **Time interval between index test(s)**: appear to be consecutively applied
Comparative	
Notes	-

Unlu 2014 (*Continued*)

Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
Are the included patients and chosen study setting appropriate?	No		
Did the study avoid including participants with multiple lesions?	Yes		
		High	**High**
DOMAIN 2: Index Test Visual Inspection - in-person			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Unclear		
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
Was the test applied and interpreted in a clinically applicable manner?	Yes		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		

Was the test interpretation carried out by an experienced examiner?	Unclear		
		Unclear	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?			

If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			
		Unclear	

Viglizzo 2004

Study characteristics	
Patient sampling	**Study design**: CS **Data collection**: NR **Period of data collection**: NR **Country**: Italy
Patient characteristics and setting	**Inclusion criteria**: PSLs examined at the Dermoscopy Service and undergoing excision; a modified version of Kenet's risk stratification approach for dermoscopy (Ascierto 2000) was used to select high- and very high-risk lesions for excision; medium- and low-risk lesions were excised based on cosmetic or functional reasons. (We extracted 2x2 data for melanocytic subgroup only) **Setting**: specialist unit (skin cancer clinic/PLC) dermoscopy service at a university department (Department of Endocrinologic and Metabolic Disease) **Prior testing**: clinical suspicion of malignancy without dermatoscopic suspicion **Setting for prior testing**: specialist unit (skin cancer clinic/PLC) **Exclusion criteria**: none reported **Sample size (participants)**: number eligible: 349 patients; number included: NR **Sample size (lesions)**: number eligible: 520 lesions; number included: 79 lesions excised included in the final analysis **Participant characteristics**: none reported **Lesion characteristics**: none reported
Index tests	**VI**: no algorithm **Method of diagnosis:** in-person diagnosis **Prior test data**: unclear **Other test data**: dermoscopy undertaken by same clinician(s) subsequent to clinical evaluation **Diagnostic threshold**: NR; correct diagnosis of melanoma **Diagnosis based on**: single observer (n = NR; "All dermoscopic evaluations were performed by the same operators") **Observer qualifications**: NR; "each lesion was ... diagnosed clinically and dermoscopically" at the dermoscopy service **Experience in practice**: not described **Experience with dermoscopy**: not described; assumed high as diagnosis at 'Dermoscopy service' **Dermoscopy:** evaluated in same study; no algorithm
Target condition and reference standard(s)	**Reference standard**: histological diagnosis alone **Target condition (final diagnoses)** Melanoma (invasive): 11; melanoma (in situ): 1

	Melanocytic lesion: 67		
Flow and timing	**Excluded participants**: none reported **Time interval to reference test**: NR		
Comparative			
Notes	-		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Are the included patients and chosen study setting appropriate?	No		
Did the study avoid including participants with multiple lesions?	Unclear		
		Unclear	**High**
DOMAIN 2: Index Test Visual Inspection - in-person			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Unclear		
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of			

the others?			
Was the test applied and interpreted in a clinically applicable manner?	Yes		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpretation carried out by an experienced examiner?	Unclear		
		Unclear	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		

If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?			
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			
		Unclear	

Walter 2012

Study characteristics	
Patient sampling	**Study design:** RCT (control group only included) **Data collection**: prospective **Period of data collection**: March 2008-May 2010 **Country**: UK
Patient characteristics and setting	**Inclusion criteria**: adults with any suspicious PSL, i.e. any lesion presented by a patient, or opportunistically seen by a family doctor or practice nurse, that could not immediately be diagnosed as benign and about which the patient could not be reassured **Setting**: primary. 15 general practices in eastern England **Prior testing**: clinical suspicion of malignancy without dermatoscopic suspicion **Setting for prior testing**: primary **Exclusion criteria**: those unable to give informed consent or considered inappropriate to include by their family doctor **Sample size (participants)**: number eligible: 1297; number included: 1293 **Sample size (lesions)**: number eligible: 1580; number included: 1583 **Participant characteristics**: mean age: 44.6 years (SD 16.8). Male: 465 (36%). Ethnicity: white 1214 (93.9%); mixed 45 (3.5%); missing: 34 (2.6%) **Lesion characteristics**: lesion thickness $\leq$ 1 mm: in 'more than half' of MM
Index tests	**VI**: Glasgow/MacKie revised 7-point checklist (MacKie 1990) **Method of diagnosis:** in-person diagnosis **Prior test data:** N/A **Diagnostic threshold**: NR **Diagnosis based on**: single observer (n = 30) **Observer qualifications:** 28 GPs and 2 nurse practitioners recruited as 'lead clinicians' (2 per practice); appears as though they conducted all skin examinations. Excluded GPs with known dermatological expertise, e.g. current hospital practitioners, clinical assistants in dermatology, and

	GPs with a special interest in dermatology **Experience in practice**: mixed GP experience, median of 15 years' experience (range 4-27 years) ; assumed low experience with PSLs. 7 had undergone some training in dermatology: 3 had a short dermatology training post, 3 were on clinical attachment to an out-patient clinic, and 1 was unspecified
Target condition and reference standard(s)	**Reference standard**: histological diagnosis plus follow-up and expert opinion Histology (not further described) 215 (histology result missing in further 4) Disease positive: 35; disease negative: 180 Clinical follow-up plus histology of suspicious lesions: 22 of the 411 referred patients were monitored (not further described); 566 of the 1162 not referred underwent expert review and were then re-assessed at 3-6 months Disease positive: 1; disease negative: 588 Expert opinion. Reviewed by 2 dermatology experts using the recorded clinical history and examination, a digital photograph, and MoleMate image where available Disease positive: 0; disease negative: 725 **Target condition (final diagnoses)** Melanoma (invasive): 30; melanoma (in situ): 6; BCC: 10 'Benign' diagnoses: 1306
Flow and timing	**Excluded participants:** 417 withdrew from control group after randomisation. 10 did not attend for dermatology assessment; 19 excluded; 1 died; 4 missing histology (in referred group; included as benign?); plus 12 with unknown outcome (in non-referred group, assumed benign and included) **Time interval to reference test**: suspicious lesions referred under 2-week wait system
Comparative	
Notes	-

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Are the included patients and chosen study setting appropriate?	Yes		

Did the study avoid including participants with multiple lesions?	No		
		Low	**High**
DOMAIN 2: Index Test Visual Inspection - in-person			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
Was the test applied and interpreted in a clinically applicable manner?	Yes		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		
Was the test interpretation carried out by an experienced examiner?	No		
		Low	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	No		
Were the reference standard results interpreted without knowledge of the results of the index tests?	No		

Expert opinion (with no histological confirmation) was not used as a reference standard	No		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		High	**High**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	No		
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?	Yes		
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			
		High	

Westerhoff 2000

Study characteristics	
Patient sampling	**Study design**: CCS (for lesion selection; study was an RCT of dermoscopy training for PCPs) **Data collection**: retrospective **Period of data collection**: NR **Country**: Australia

Westerhoff 2000 (*Continued*)

Patient characteristics and setting	**Inclusion criteria**: clinically atypical PSLs; 50 invasive melanomas and 50 nonmelanomas randomly selected from the Sydney Melanoma Unit PSL image database **Setting**: specialist unit (lesion selection) **Prior testing**: selected for excision or followed up **Setting for prior testing**: specialist unit (skin cancer clinic/PLC) **Exclusion criteria**: none reported **Sample size (participants)**: number included: NR **Sample size (lesions)**: number included: 100 **Participant characteristics**: none reported **Lesion characteristics:** median Breslow thickness 0.6 mm
Index tests	**VI**: no algorithm **Method of diagnosis**: clinical photographs **Prior test data**: unclear; all participants "were instructed not to look at the surface microscopic image until they had scored the clinical image" **Diagnostic threshold**: NR **Diagnosis based on**: average (n = 37); 74 practising primary care practitioners randomised to dermoscopy education intervention or not. Diagnoses were recorded for both groups of GPs at baseline (pre-test) and after the training intervention had been administered to the intervention group (post-test), resulting in 8 sets of 2x2 data based on interpretation of the same set of 100 lesions; post-test data for the intervention group of GPs was used for the VI analysis **Observer qualifications:** GP **Experience in practice**: considered to be low; only practitioners who had had no formal training with surface microscopy and did not use a surface microscope in their clinical practice were included **Experience with dermoscopy**: low experience/novice users (non-training arm); 'trained' for the intervention arm **Other detail**: camera designed for close-up clinical photography (Elicar Macrolens, Japan) **Dermoscopy:** evaluated in same study; Menzies criteria (intervention arm underwent training in Menzies criteria)
Target condition and reference standard(s)	**Reference standard**: histological diagnosis plus follow-up Histology: all the lesions except 2 had been excised after photography and subjected to histopathological examination Disease positive: 50; disease negative: 48 Clinical follow-up plus histology of suspicious lesions: the 2 benign PSLs that had not been excised were monitored over a longer period of time and had shown no morphological change Length of follow-up: NR; disease positive: 0; disease negative: 2 **Target condition (final diagnoses)** Melanoma (invasive): 50; 'benign' diagnoses: 50
Flow and timing	**Excluded participants:** none reported **Time interval to reference test:** "All the lesions except two had been excised after photography"
Comparative	
Notes	-
Methodological quality	

Westerhoff 2000 (*Continued*)

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	No		
Did the study avoid inappropriate exclusions?	Unclear		
Are the included patients and chosen study setting appropriate?	No		
Did the study avoid including participants with multiple lesions?	Unclear		
		High	**High**
DOMAIN 2: Index Test Visual inspection - image-based			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Unclear		
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
Was the test applied and interpreted in a clinically applicable manner?	No		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		

Was the test interpretation carried out by an experienced examiner?	Yes		
		Unclear	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	Yes		
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?	Unclear		

Westerhoff 2000 (*Continued*)

If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			
		High	

Winkelmann 2016

Study characteristics	
Patient sampling	**Study design**: CCS **Data collection**: retrospective image selection/prospective interpretation **Period of data collection**: NR **Country**: NR
Patient characteristics and setting	**Inclusion criteria**: images of PSLs previously analysed by a digital classifier MSDSLA; method of selection of the 12 NR **Setting**: dermoscopy conference **Prior testing**: NR **Setting for prior testing**: unspecified **Exclusion criteria**: none reported **Sample size (participants)**: NR **Sample size (lesions)**: number included: 12 **Participant characteristics**: none reported **Lesion characteristics**: none reported
Index tests	**VI**: no algorithm **Method of diagnosis**: clinical photographs **Prior test data**: unclear **Other test data**: dermoscopic images presented to observer subsequent to diagnosis using clinical images alone **Diagnostic threshold**: NR, biopsy decision **Diagnosis based on**: average (n = 70) **Observer qualifications**: dermatologist **Experience in practice**: not described; recruited "dermatologists at a dermoscopy conference"; no further details **Other detail**: study authors report that practitioners with a particular interest in skin cancer or technology may have chosen to attend this conference and/or self-selected to take part in the study **Dermoscopy:** evaluated in same study; no algorithm
Target condition and reference standard(s)	**Reference standard**: histological diagnosis alone Disease positive: 5; disease negative: 7 **Target condition (final diagnoses)** Melanoma (invasive): 3; melanoma (in situ): 2 Mild/moderate dysplasia: 7 low-grade dysplastic naevi

Flow and timing	**Excluded participants**: none reported **Time interval to reference test**: NR		
Comparative			
Notes	-		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	No		
Did the study avoid inappropriate exclusions?	Unclear		
Are the included patients and chosen study setting appropriate?	No		
Did the study avoid including participants with multiple lesions?	Unclear		
		High	**High**
DOMAIN 2: Index Test Visual inspection - image-based			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Unclear		
For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			

Was the test applied and interpreted in a clinically applicable manner?	No		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpretation carried out by an experienced examiner?	Unclear		
		Unclear	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		

If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?	Yes		
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			
		Unclear	

Zaumseil 1983

Study characteristics	
Patient sampling	**Study design**: CS **Data collection**: NR **Period of data collection**: 1976-1981 **Country**: Germany
Patient characteristics and setting	**Inclusion criteria**: skin lesions undergoing excision **Setting**: secondary (not further specified) **Prior testing**: selected for excision (no further detail) **Setting for prior testing**: specialist unit (skin cancer clinic/PLC) Described as 'skin clinic' **Exclusion criteria**: disagreement between evaluators on tumour histological classification. Those in which the histological diagnosis was 'unclear' were excluded, melanoma metastases were excluded **Sample size (participants)**: NR **Sample size (lesions)**: number included: 7063 **Participant characteristics**: none reported **Lesion characteristics**: none reported
Index tests	**VI**: no algorithm **Method of diagnosis:** in-person diagnosis **Prior test data:** N/A, in-person diagnosis **Diagnostic threshold**: primary diagnosis of melanoma (method of Kopf 1975 was cited) **Diagnosis based on**: single observer (n = NR) **Observer qualifications**: NR **Experience in practice**: not described **Experience with index test**: not described

Zaumseil 1983 (*Continued*)

Target condition and reference standard(s)	**Reference standard**: histological diagnosis alone Disease positive: 337; disease negative: 6726 **Target condition (final diagnoses)** Melanoma (invasive or in situ): 337 Other diagnoses only listed for the 89 false-positives: 23 benign naevi; 13 BCC; 12 blue nevus; 11 angiomatosis; 10 SK; 6 histiocytoma; 4 Spitz nevus; 4 lentigo; 3 Bowen's disease; 1 acrospiroma; 1 keratinizing papilloma		
Flow and timing	**Excluded participants**: none reported **Time interval to reference test**: NR		
Comparative			
Notes	-		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
Are the included patients and chosen study setting appropriate?	No		
Did the study avoid including participants with multiple lesions?	Unclear		
		High	**High**
DOMAIN 2: Index Test Visual Inspection - in-person			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		

For studies reporting the accuracy of multiple diagnostic thresholds, was each threshold or algorithm interpreted without knowledge of the results of the others?			
Was the test applied and interpreted in a clinically applicable manner?	Yes		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpretation carried out by an experienced examiner?	Unclear		
		Low	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Expert opinion (with no histological confirmation) was not used as a reference standard	Yes		
Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		

Zaumseil 1983 (*Continued*)

Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
If the reference standard includes clinical follow-up of borderline/benign appearing lesions, was there a minimum follow-up following application of index test(s) of at least: 3 months for melanoma or cSCC or 6 months for BCC?			
If more than one algorithm was evaluated for the same test, was the interval between application of the different algorithms 1 month or less?			
		Unclear	

ABCD(E): asymmetry, border, colour, differential structures (enlargement); **AK**: actinic keratosis; **AMN**: atypical MN; **BCC**: basal cell carcinoma; **CAD**: computer-assisted diagnosis; **CCS**: case-controlled study; **CD**: compact disc; **CM**: cutaneous melanoma; **CMM**: cutaneous malignant melanoma; **CS**: case series; **cSCC**: cutaneous squamous cell carcinoma; **DF**: dermatofibroma; **ELM**: epiluminescence microscopy; **FN**: false-negative; **FP**: false-positive; **GP**: general practitioner; **H&E**: haematoxylin and eosin stain; **LPLK**: lichen planus-like keratosis; **LS**: lentigo simplex; **MM**: malignant (invasive) melanoma; **MN**: melanocytic naevi; **MSDSLA**: multispectral digital skin lesion analysis device; **N/A**: not applicable; **NMLs**: non-melanocytic lesions; **NR**: not reported; **PCPs**: primary care providers; **PLC**: pigmented lesion clinic; **PSL**: pigmented skin lesion; **RCM**: reflectance confocal microscopy; **RCT**: randomised controlled trial; **SCC**: squamous cell carcinoma; **SD**: standard deviation; **SDDI**: short-term sequential digital dermoscopy imaging; **SK**: seborrhoeic keratosis; **SSM**: superficial spreading melanoma; **SVS**: support vector system; **VI**: visual inspection; **7FFM**: seven features for melanoma

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abbasi 2004	Not a primary study; systematic review
Aldridge 2011a	Ineligible test observer: medical students and lay people
Aldridge 2011b	Ineligible test observer

(*Continued*)

Aldridge 2013	Unable to construct 2x2 table based on data presented. Not test accuracy study
Alendar 2009	Ineligible reference standard. Only 7 reported verified histologically
Argenziano 1999	Ineligible study population. Only included melanoma
Argenziano 2003	Unable to construct 2x2 table based on data presented. Table V gives se/sp data for 108 lesions but cannot derive the number of melanoma for this subset of the original 128 Contacted study authors 10 May 2016; 24 June 2016
Argenziano 2012	Ineligible reference standard. No follow-up of test-negatives
Argenziano 2014	Unable to construct 2x2 table based on data presented
Ascierto 2003	Not a primary study
Badertscher 2015	Unable to construct 2x2 table based on data presented
Bafounta 2001	Not a primary study, systematic review
Banky 2005	Ineligible target condition Ineligible index test
Basarab 1996	Ineligible study population. Not all suspected of skin cancer Unable to construct 2x2 table based on data presented
Bauer 2000	Ineligible index test. Does not provide 2x2 data for VI alone
Bauer 2005	Ineligible index test, follow-up/monitoring study
Becker 1954	Not a primary study
Benelli 2000	Unable to construct 2x2 table based on data presented. Only inter-rater reliability data given (n = 25); study authors have published much larger evaluations of 7FFM and ABCD
Blum 2004a	Not a primary study, comment paper
Blum 2004b	Not a primary study, letter. Only limited data presented. Evaluates '3-colour' rule as developed by Mackie 2002 (excluded as assessment of individual lesion features only)
Blum 2004c	Ineligible index test, evaluates dermoscopy only
Bolognia 1990	Ineligible reference standard, no reference standard diagnosis for index test-negatives
Bono 2001	Unable to construct 2x2 table based on data presented. Aim of the study was to determine what features are present in amelanotic cutaneous melanoma

(*Continued*)

Borsari 2015	Individual lesion characteristics
Borve 2012	Ineligible study population, included participants without skin lesions Ineligible sample size, < 5 BCC
Brown 2000	Not a primary study, systematic review
Brown 2009	Ineligible test observer, lay people
Buhl 2012	Ineligible index test, follow-up/monitoring Duplicate or related publication, same participants as Haenssle 2010
Burki 2015	Not a primary study
Burr 2015	Not a primary study
Burton 1998	Ineligible reference standard Unable to construct 2x2 table based on data presented, can only get 2x2 data for referral accuracy
Carli 2003b	Ineligible reference standard. Only 39/1042 with reference test
Carli 2003c	Ineligible sample size
Carli 2004a	Ineligible sample size, < 5 MM per arm Unable to construct 2x2 table based on data presented
Carli 2004b	Ineligible index test Study author passed away; unable to make contact with co-authors
Carli 2004c	Ineligible index test, 'clinical diagnosis'. Dataset covers 1997-2001, but dermoscopy routinely introduced 1998; study authors contacted but no response
Carli 2005	Unable to construct 2x2 table based on data presented. Only sensitivity data given (% with correct diagnosis); % of benign lesions incorrectly diagnosed was not reported We will try to contact study authors.
Carlos-Ortega 2007	Unable to construct 2x2 table based on data presented. Gives se/sp for VI and dermoscopy in the English abstract. 68 patients/70 lesions were included but only 36 seem to have had VI results and all underwent dermoscopy. 2 observers performed each test blinded to each other. Table I gives 22 with BCC and 11 with melanoma overall (number D+ not reported for those with VI results), but using either or both of these numbers with the se/sp provided does not give the same PPV and NPV as given by the study authors Data not clearly presented for 2x2; translator suggested alternative but still does not work out to what is in paper; tried contacting authors twice, no reply
Chen 2001	Not a primary study, systematic review comparing PCP accuracy with dermatologist accuracy
Chen 2006	Unable to construct 2x2 table based on data presented, only given AUC

(*Continued*)

Chiaravalloti 2014	Ineligible study population, included melanoma only
Ciudad-Blanco 2014	Ineligible study population, included melanoma only
Cooper 2002	Ineligible target condition, insufficient data for inclusion in melanoma review
Cornell 2015	Ineligible test observer
Cox 2008	Ineligible reference standard. Se and sp estimates for diagnosis of melanoma for both the 7-point checklist and the revised (10-point) checklist; reference standard not reported for any of the 381 TWR referrals for melanoma Study author contacted 10 May 2016; co-author contacted 24 June 2016
De Giorgi 2011	Duplicate publication. Study appears to use same lesions as Carli 2003a (included study). Both studies have the same numbers of melanomas and benign nevi and have common co-authors (De Giorgi 2011 in particular). Although not explicit, the De Giorgi 2011 paper appears to have used the same lesions and study design but with different observers. The original Carli 2003b paper reported using 8 expert observers while the later paper recruited 8 dermatologists who had undergone a dermoscopy training course but who reported no experience in assessing pigmented skin lesions
DeCoste 1993	Unable to construct 2x2 table based on data presented. Not given the total number of D+/D- or total number of lesions included. Just given the se/sp values
Di Carlo 2014	Ineligible index test. Videothermography not relevant for the review and there is no 2x2 data for dermoscopy if derivation study. Only included AK and BCC
Di Chiacchio 2010	Ineligible target condition, excluded nail bed melanoma Unable to construct 2x2 table due to insufficient data to extract
Dreiseitl 2009	Ineligible index test. Did not evaluate VI alone
Duff 2001	Ineligible index test. Did not evaluate VI alone
Edmondson 1999	Ineligible reference standard. It seems that the reference standard here was expert diagnosis. This is not a teledermatology paper
Emmons 2011	Unable to construct 2x2 table based on data presented. Not test accuracy study; promoted primary prevention
Engelberg 1999	Ineligible sample size, only 1 confirmed melanoma and 3 BCC
English 2003	Unable to construct 2x2 table based on data presented. No accuracy data given
English 2004	Unable to construct 2x2 table based on data presented. No accuracy data
Fabbrocini 2008	Unable to construct 2x2 table because insufficient data provided for each index test to populate 2x2 table Contacted study authors to request cross-tabulation of each clinician's diagnosis (e.g. at threshold of ≥ 3

(*Continued*)

	on 7-point checklist) against the histological diagnosis or a cross-tabulation of the remote diagnosis against the face-to-face diagnoses, or both. Study author responded 30 June 2016, cannot access data needed
Federman 1995	Unable to construct 2x2 table based on data presented. Not test accuracy study
Fikrle 2013	Ineligible reference standard. Follow-up study < 50% of study participants had their final diagnosis reached by histopathology
Freeman 1963	Unable to construct 2x2 table based on data presented. Only gives % correct for each lesion type Tables 2 and 3 appear to give % correct diagnoses per lesion type, but do not give data on numbers misclassified as melanoma, or other malignancy, i.e. FPs Contacted study authors who responded; paper too old, cannot provide data
Friedman 1985	Not a primary study
Funt 1963	Ineligible index test. No 2x2 data to construct 2x2 table
Gerbert 1996	Ineligible target condition. No breakdown of final diagnoses for included lesions Unable to construct 2x2 table based on data presented Only gives % correct for each lesion type; not se/sp
Gerbert 1998	Unable to construct 2x2 table based on data presented
Giannotti 2004	Not a primary study, a review
Grana 2003	Ineligible index test. Individual lesion characteristics, only looking at lesion border
Grob 1998	Not a primary study
Guibert 2000	Ineligible reference standard. Not designed as an accuracy study only observational. Cannot get 2x2 data > 50% of study participants did not receive histology as ref standard
Gunduz 2003	Ineligible sample size, case study
Gutierrez 2013	Ineligible index test, test to improve histopathology diagnosis
Hacioglu 2013	Ineligible target condition. Does not provide sufficient data for detection of melanoma
Haenssle 2010	Ineligible index test. Test used for monitoring and not initial diagnosis; no VI data
Haenssle 2010a	Unable to construct 2x2 table based on data presented. Does not report specificity Duplicate or related publication, same participants as Haenssle 2010
Hallock 1998	Ineligible index test. 'Clinical diagnosis'; dermoscopy used for 3 of the 4 years of study recruitment
Haniffa 2007	Ineligible reference standard, looks like approximately 20% of participants received a final diagnosis by histology. 179 biopsies were performed. Total sample was 881 lesions

(*Continued*)

Har-Shai 2001	Ineligible index test, 'clinical diagnosis'
Heal 2008	Unable to construct 2x2 table based on data presented. Sensitivities and PPVs are given so theoretically a 2x2 could be worked out, but the numbers do not appear to work out Author response: the 2x2 table the Cochrane researchers want to create is not possible for our results, because sensitivity and PPV are based on different sample sizes
Healsmith 1994	Ineligible reference standard. Benign lesions described as 'clinically diagnosed' rather than histology/follow-up
Higgins 1992	Ineligible study population, included only benign lesions Ineligible sample size, no melanomas Unable to construct 2x2 table based on data presented, no malignant cases
Hoorens 2016	Ineligible index test Ineligible reference standard. No information on numbers undergoing histology; and no follow-up reported for benign-appearing lesions Unable to construct 2x2 table based on data presented
Huang 1996	Individual lesion characteristics. Border irregularity not overall diagnosis Unable to construct 2x2 table based on data presented
Jamora 2003	Ineligible reference standard. No reference standard for index test-negatives
Janda 2014	Ineligible sample size, only 1 case of melanoma, 1 case of BCC and 1 of SCC
Jensen 2015	Not a primary study, comment paper
Jolliffe 2001	Ineligible index test. Provides data for clinical diagnosis (including dermoscopy for some cases)
Jonna 1998	Unable to construct 2x2 table based on data presented, only included index test-positives to get PPV
Kaddu 1997	Ineligible sample size. Sample size < 5; not test accuracy
Keefe 1990	Ineligible reference standard. Only 28% (60/214) of non-melanoma group had excision
Kelly 1986	Ineligible target condition. Cannot disaggregate the severely dysplastic/in situ MM Ineligible sample size, unclear whether > 5 in situ melanoma
Koh 1990	Ineligible reference standard, screening study; no adequate reference standard
Kroemer 2011	Ineligible index test, provides data for clinical diagnosis (including dermoscopy for some cases)
Krol 1991	Ineligible reference standard. No follow-up reported for those who were test-negative

(*Continued*)

Kurvers 2015	Ineligible index test. Collective intelligence - majority rule and quorum rule applied to large number of test interpreter decisions Duplicate or related publication, re-analyses data from 2 previously published studies to determine whether collective intelligence (i.e. majority rules or quorum rules across a large number of observers) improves test accuracy. We have excluded one of these studies as it did not provide the number of melanomas (Argenziano 2003) and included the other in our dermoscopy review (Zalaudek 2006).
Kvedar 1997	Ineligible study population. Not all suspected of skin cancer
Lechner 2015	Not a primary study, erratum
Lewis 1999	Unable to construct 2x2 table based on data presented. Study appears to meet all eligibility criteria but disease prevalence not given alongside se/sp Contacted study authors 10 May 2016; email returned
Lindelöf 1994	Ineligible study population, only malignant melanoma Unable to construct 2x2 table based on data presented. Not enough information given to derive a 2x2 table. Only given for a sample of 50 participants who had a strong suspicion of melanoma clinically. Do not know what happened to those with no suspicion clinically
Lorentzen 2000	Ineligible index test. Does not provide data for VI alone
Luttrell 2012	Ineligible test observer. Accuracy data only given for lay-people, not interested in this population of test observers
Machet 2005	Ineligible study population. (Note: this is a staging study)
MacKenzie-Wood 1998	Ineligible study population, only malignant diagnosis
MacKie 1990	Not a primary study
Mackie 1991	Not a primary study, letter
Mackie 2002	Individual lesion characteristics, presence of ≥ 3 colours on dermoscopy
Mahendran 2005	Ineligible index test. Face to face was 'clinical diagnosis', i.e. VI +/- use of dermoscopy
Mahon 1997	Not a primary study, a summary of a comparison of 2 screening checklists
Malvehy 2014	Ineligible index test. Does not report data for VI alone
Marghoob 1995	Not a primary study, letter
Marghoob 2007	Not a primary study
Markowitz 2015	Ineligible target condition. Does not report sufficient data for detection of melanoma

(*Continued*)

McCarthy 1995	Not a primary study, leaflet
McMullan 1956	Unable to construct 2x2 table based on data presented
Menzies 2008	Ineligible index test, evaluated dermoscopy alone
Menzies 2011	Ineligible index test, surveillance study; data used to id factors predictive of lesion changes
Menzies 2013	Ineligible index test, evaluated dermoscopy only
Moffatt 2006	Ineligible index test, 'clinical diagnosis'
Mohammad 2015	Ineligible study population, only included BCC
Morrison 2001	Unable to construct 2x2 table based on data presented Study gives % correct diagnosis within each histology group and then gives the % 'correct' diagnosis of skin cancer as 22% for FP and 87% for dermatologist. But these statistics appear to have been reached by taking the mean of the % correct diagnoses across the malignant groups and do not equate to sensitivity. i.e. If you take the mean of the FP correct (%) for the 4 malignant groups you get: (40 + 22 + 25 + 0) / 4 = 21.75% and then the same for the dermatologist correct (%) column: (95 + 77 + 75 + 100)/4 = 86.75%
Nachbar 1994	Ineligible index test. Data for VI alone influenced by use of dermoscopy in most cases
Nathansohn 2007	Unable to construct 2x2 table based on data presented. Not test accuracy; follow-up study
Nilles 1994	Ineligible index test. Does not provide data for VI alone
Osborne 1998	Ineligible reference standard. Not clear what the ref standard is Unable to construct 2x2 table based on data presented
Osborne 1999	Ineligible study population. Only patients with melanoma included
Parslew 1997	Ineligible study population. Not all suspected of skin cancer
Pazzini 1996	Unable to construct 2x2 table based on data presented
Perednia 1992	Unable to construct 2x2 table based on data presented. Not test accuracy
Perrinaud 2007	Ineligible index test. Does not provide data for VI alone
Piccolo 2000	Ineligible index test. No data can be extracted for VI alone
Piccolo 2002	Not a primary study Not enough data to populate 2x2 table. No breakdown of index test results and ref standard

(*Continued*)

Pizzichetta 2001	Unable to construct 2x2 table based on data presented. Observer agreement only
Provost 1998	Unable to construct 2x2 table based on data presented. Not test accuracy; only reports concordance
Quereux 2011	Ineligible index test, self-administered questions to patients attending a GP surgery before their appointment to determine whether they were at high risk of melanoma, which is meant to highlight to the GP which patient to examine during their consultation
Rallan 2006	Ineligible index test. No data can be extracted for VI alone
Rampen 1988	Ineligible study population. Only melanoma included
Reeck 1999	Ineligible study population. Only included index test-negatives; i.e. those considered benign by referring clinician Ineligible target condition
Riddell 1961	Ineligible study population. All malignant
Rigel 1993	Not a primary study
Robati 2014	Ineligible reference standard. No follow-up of participants not referred to dermatology clinics, who did not receive histopathology
Robinson 2010	Ineligible index test, self examination
Rosado 2003	Not a primary study, systematic review
Rossi 2000	Ineligible reference standard. Unclear reference standard in disease-negative
Roush 1986	Ineligible target condition, only dysplastic naevus
Salvio 2011	Not a primary study Ineligible sample size
Schindewolf 1994	Ineligible index test, evaluated CAD not VI
Schmoeckel 1987	Not a primary study
Schwartzberg 2005	Ineligible target condition, does not provide sufficient data for detection of melanoma
Seidenari 2006	Ineligible study population. Assessed best means of follow-in up patients with previous melanoma - total body exam versus only lesions > 2 cm. No melanoma identified
Seidenari 2006a	Individual lesion characteristics. Looks like this study is only looking at asymmetry judgement
Shariff 2010	Ineligible reference standard

(*Continued*)

Sondak 2015	Not a primary study, comment paper
Soyer 2004	Ineligible index test. Does not provide data for VI alone
Stanganelli 1998b	Unable to construct 2x2 table based on data presented. Cannot derive specificity; only gives exact diagnoses for MM and 2 benign categories and not number benign misdiagnosed as MM
Stanley 2003	Individual lesion characteristics. Fuzzy histogram based on the lesion's colour, which is an individual lesion characteristic
Stathopoulos 2015	Unable to construct 2x2 table based on data presented. Only included index test-positive patients, i.e. no FN or TN results
Stratigos 2007	Ineligible reference standard Unable to construct 2x2 table based on data presented
Tandjung 2015	Ineligible target condition. 'Malignant' included: AK, Bowen's, dysplastic nevus, lentigo maligna, SCC, BCC, MM, keratoacanthoma Ineligible index test. GPs sent images for telederm opinion; then free to send for biopsy or not; results shown are only for those that were biopsied, according to TD advice
Terrill 2009	Ineligible index test. Whole body skin examination after participants referred on for further assessment by a specialist Unable to construct 2x2 table based on data presented
Terushkin 2010a	Unable to construct 2x2 table based on data presented. Not test accuracy, reports final diagnoses of those excised over a number of time periods and benign-malignant ratio
Terushkin 2010b	Unable to construct 2x2 table based on data presented. Not test accuracy - reports final diagnoses of those excised over a number of time periods and benign-malignant ratio
Thomson 2005	Not a primary study, letter
Torrey 1941	Ineligible target condition, included non-cutaneous lesions
Ulrich 2015	Ineligible target condition. Does not provide sufficient data for evaluation of melanoma
Van der Rhee 2010	Ineligible reference standard.< 50% of disease-negative have an adequate reference standard
Van der Rhee 2011	Ineligible sample size, < 5 cases
Vasili 2010	Conference abstract
Wagner 1985	Unable to construct 2x2 table based on data presented
Walter 2010	Not a primary study, clinical trial protocol

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Walter 2013	Ineligible reference standard. Final diagnosis reached by histology or expert opinion; no follow-up of non-excised lesions reported in this paper. The Walter 2012 trial report does report follow-up for enough benign lesions for control arm (weighted 7-point checklist) data to be included. Study authors contacted and confirmed calculations (2 March 2016)
Warshaw 2009a	Unable to construct 2x2 table based on data presented. Study presents diagnostic accuracy of teledermatology and clinic diagnosis in comparison to histopathology; in order to include in our review, data would need to be presented as a 2x2 contingency table, either per type of malignancy e.g. tele-diagnosis classification of melanoma vs not melanoma against histological diagnosis of melanoma/not melanoma, or with malignant diagnoses grouped together, ie tele-diagnosis of malignancy vs not malignant against same histological breakdown Study authors contacted: "the 2x2 table the Cochrane researchers want to create is not possible for our results, because sensitivity and PPV are based on different sample sizes. This can be seen in Table 2 of the paper which actually adds up to 11870 skin lesions across, as for each histological diagnosis of interest the first lesion with such a histological diagnosis was considered per patient. Hence, a patient might appear several times across the columns. Table 1 adds up to 8585 skin lesions - the first skin lesion in the data set per patient with a clinical diagnosis."
Warshaw 2009b	Unable to construct 2x2 table based on data presented, as per Warshaw 2009a
Warshaw 2010	Unable to construct 2x2 table based on data presented, as per Warshaw 2009a; this 2010 paper presents combined data for pigmented and nonpigmented lesions
Westbrook 2006	Unable to construct 2x2 table based on data presented
Whitaker-Worth 1998	Ineligible study population Ineligible test observer, mixed medical student/clinicians Unable to construct 2x2 table based on data presented, not test accuracy study
Whited 1998	Ineligible sample size
Williams 1991	Unable to construct 2x2 table based on data presented
Winkelmann 2015a	Duplicate or related publication
Winkelmann 2015b	Duplicate or related publication
Wolf 1998	Ineligible index test, clinical diagnosis study. Test clearly described, "concerning the clinical diagnosis, we were not able to ascertain from the clinical data sheet whether the referring physicians used additional diagnostics techniques such as dermoscopy"
Yoo 2015	Conference abstract
Youl 2007a	Ineligible index test, 'clinical diagnosis' - dermoscopy used in some but not all cases Response from study author, "One of the main issues is that we just don't know to what extent dermoscopy was used in that study. We just asked where they used it in a general sense and not for each case. However for each case GPs and skin clinic doctors did indicate whether they conducted a whole- or part-body skin examination (or just lesion specific)

(*Continued*)

Youl 2007b	Ineligible index test. Evaluates clinical diagnosis (some lesions had dermoscopy)
Zaballos 2013	Ineligible study population. They do not have enough benign cases to include as full report
Zou 2001	Not a primary study. Study uses results from Stolz 1994 Unable to construct 2x2 table based on data presented. Just showing ROC curves

AK: actinic keratosis; **AUC**: area under the curve; **BCC** - basal cell carcinoma; **CAD**: computer assisted diagnosis; **D+/D-**: disease-positive/disease-negative; **7FFM**: seven features for melanoma; **FPs**: false-positives; **FN**: false-negative; **GP**: general practitioner; **PCP** - primary care provider; **PPV**: positive predictive value; **MM**: malignant (invasive) melanoma; **NPV**: negative predictive value; **ref**: reference; **SCC**: squamous cell carcinoma; **se/sp**: sensitivity/specificity; **TD**: teledermatology; **TN**: true negative; **TWR**: two week rule; **VI**: visual inspection

DATA

Presented below are all the data for all of the tests entered into the review.

Tests. Data tables by test

Test	No. of studies	No. of participants
1 Visual inspection - in-person (MM)	7	6857
2 Visual inspection - image-based (MM)	5	599
3 Visual inspection - in-person (MEL)	28	25604
4 Visual inspection - image-based (MEL)	11	1243
5 Visual inspection - in-person (Any)	7	8091
6 Visual inspection - image-based (Any)	3	547
7 MEL- VI - in-person - no algorithm	21	19330
8 MEL- VI - in-person - no algorithm (alternative thresholds)	2	475
9 MEL- VI - in-person - (A)BCD(E) at NR or standard threshold	6	5501
10 MEL-VI - in-person - ABCD at NR	2	3548
11 MEL-VI - in-person - ABCDE at ≥ 1	2	1541
12 MEL-VI - in-person - ABCDE at ≥ 2	3	1761
13 MEL-VI - in-person - ABCDE at ≥ 3	2	1541
14 MEL-VI - in-person - ABCDE at ≥ 4	2	1541
15 MEL-VI - in-person - ABCDE at ≥ 5	2	1541
16 MEL-VI - in-person - BCD at ≥ 1	1	192
17 MEL-VI - in-person - BCD at ≥ 2	1	192
18 MEL-VI - in-person - BCD at ≥ 3	1	192
19 MEL-VI - in-person - 7point at ≥ 2	1	205

20 MEL-VI - in-person - 7point at ≥ 3	1	205
21 MEL-VI - in-person - 7point at ≥ 4	1	205
22 MEL-VI - in-person - 7point(rev) at ≥ 3	1	773
23 MEL-VI - in-person - Collas at ≥ 1	1	353
24 MEL- VI - image-based - no algorithm	9	1090
26 MEL-VI - image-based - ABCD(E) at standard	2	153
27 MEL-VI - image-based - ABCD at ≥ 2	1	103
28 MEL-VI - image-based - ABCD at ≥ 3	1	103
29 MEL-VI - image-based - ABCDE at ≥ 2	1	50
30 MEL-VI - image-based - ABCDE at ≥ 3	1	50
31 MEL- VI - in-person - experience NR	12	16778
32 MEL- VI - in-person - experience high	9	3547
33 MEL- VI - in-person - experience moderate	1	567
34 MEL- VI - in-person - experience low	4	2008
35 MEL- VI - in-person - experience mixed	2	2704
36 MEL- VI - image-based - experience NR	5	663
37 MEL- VI - image-based - experience high	5	540
38 MEL- VI - image-based - experience low	1	134
39 MEL- VI - image-based - experience mixed	2	90
40 VI - in-person - expert consultant (MEL)	9	3547
41 VI - in-person - consultant (MEL)	12	16778
42 VI - in-person - resident/registrar (MEL)	2	1236
43 VI - in-person - mixed qualifications (secondary care) (MEL)	2	2704
44 VI - in-person - GP (MEL)	3	1339
45 MEL- VI - image-based - expert consultant	4	700

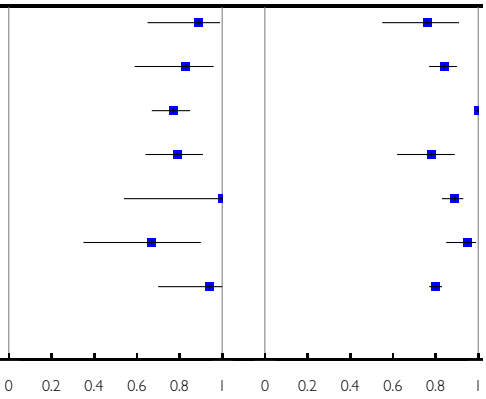
46 MEL- VI - image-based - consultant	4	200
47 MEL- VI - image-based - mixed qualifications (secondary care)	1	200
48 MEL- VI - image-based - mixed qualifications (secondary/primary care)	1	40
49 MEL- VI - image-based - mixed qualifications (primary care)	2	184
51 MEL - Selected on quality - pathway 2 or 3	5	5728
52 MEL - Selected on quality - pathway 5	9	3556

Test 1. Visual inspection - in-person (MM).

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 1 Visual inspection - in-person (MM)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Bono 1996	16	6	2	19	0.89 [0.65, 0.99]	0.76 [0.55, 0.91]
Green 1994	15	23	3	123	0.83 [0.59, 0.96]	0.84 [0.77, 0.90]
Kopf 1975	76	19	23	5420	0.77 [0.67, 0.85]	1.00 [0.99, 1.00]
Krahn 1998	31	9	8	32	0.79 [0.64, 0.91]	0.78 [0.62, 0.89]
McGovern 1992	6	21	0	165	1.00 [0.54, 1.00]	0.89 [0.83, 0.93]
Viglizzo 2004	8	3	4	52	0.67 [0.35, 0.90]	0.95 [0.85, 0.99]
Walter 2012	15	152	1	605	0.94 [0.70, 1.00]	0.80 [0.77, 0.83]

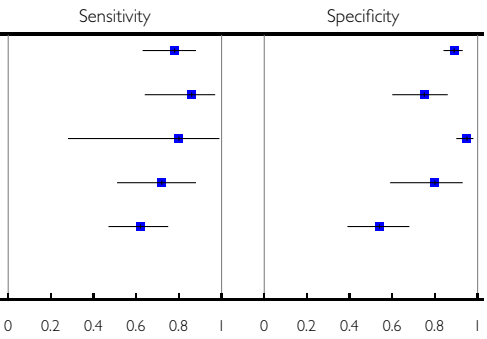


Test 2. Visual inspection - image-based (MM).

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 2 Visual inspection - image-based (MM)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Lorentzen 1999	38	20	11	163	0.78 [0.63, 0.88]	0.89 [0.84, 0.93]
Rao 1997	18	13	3	38	0.86 [0.64, 0.97]	0.75 [0.60, 0.86]
Scope 2008	4	7	1	133	0.80 [0.28, 0.99]	0.95 [0.90, 0.98]
Troyanova 2003	18	5	7	20	0.72 [0.51, 0.88]	0.80 [0.59, 0.93]
Westerhoff 2000	31	23	19	27	0.62 [0.47, 0.75]	0.54 [0.39, 0.68]

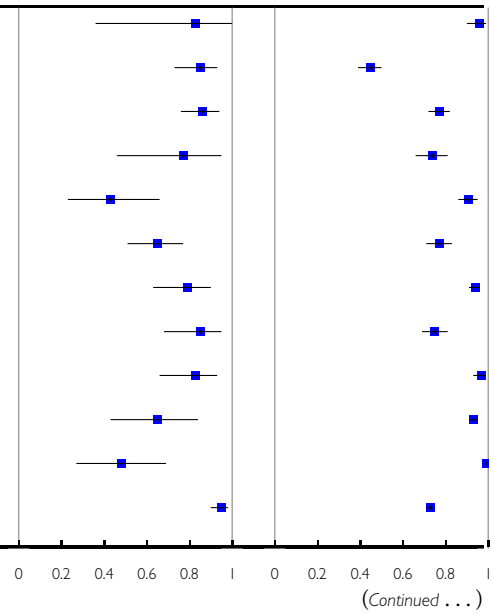


Test 3. Visual inspection - in-person (MEL).

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 3 Visual inspection - in-person (MEL)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Barzegari 2005	5	5	1	111	0.83 [0.36, 1.00]	0.96 [0.90, 0.99]
Benelli 1999	51	189	9	152	0.85 [0.73, 0.93]	0.45 [0.39, 0.50]
Bono 2002a	57	56	9	191	0.86 [0.76, 0.94]	0.77 [0.72, 0.82]
Bono 2002b	10	39	3	109	0.77 [0.46, 0.95]	0.74 [0.66, 0.81]
Bono 2006	10	16	13	167	0.43 [0.23, 0.66]	0.91 [0.86, 0.95]
Carli 2002a	35	46	19	156	0.65 [0.51, 0.77]	0.77 [0.71, 0.83]
Collas 1999	30	19	8	296	0.79 [0.63, 0.90]	0.94 [0.91, 0.96]
Cristofolini 1994	28	46	5	141	0.85 [0.68, 0.95]	0.75 [0.69, 0.81]
Cristofolini 1997	29	4	6	137	0.83 [0.66, 0.93]	0.97 [0.93, 0.99]
Dummer 1993	15	49	8	699	0.65 [0.43, 0.84]	0.93 [0.91, 0.95]
Ek 2005	11	23	12	2536	0.48 [0.27, 0.69]	0.99 [0.99, 0.99]
Gachon 2005	141	1058	8	2829	0.95 [0.90, 0.98]	0.73 [0.71, 0.74]



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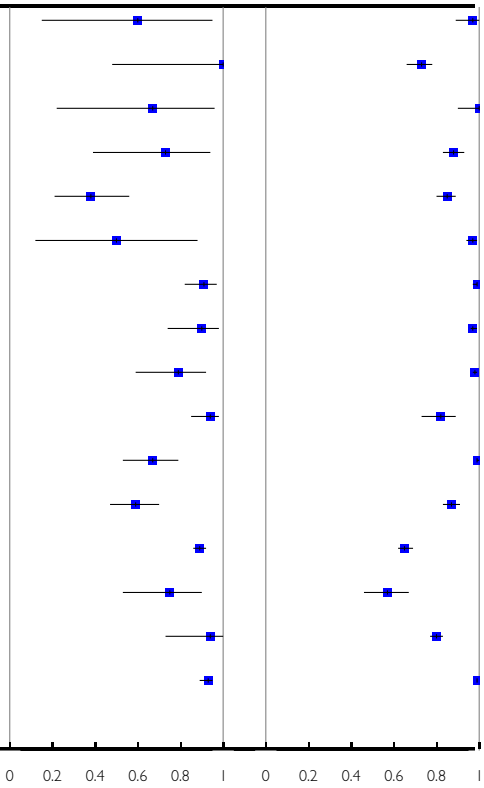
Study	TP	FP	FN	TN	Sensitivity	Specificity
Green 1991	3	2	2	63	0.60 [0.15, 0.95]	0.97 [0.89, 1.00]
Grimaldi 2009	5	63	0	167	1.00 [0.48, 1.00]	0.73 [0.66, 0.78]
Langley 2001	4	0	2	34	0.67 [0.22, 0.96]	1.00 [0.90, 1.00]
McGovern 1992	8	21	3	160	0.73 [0.39, 0.94]	0.88 [0.83, 0.93]
Menzies 2009	12	46	20	253	0.38 [0.21, 0.56]	0.85 [0.80, 0.89]
Morales Callaghan 2008	3	5	3	189	0.50 [0.12, 0.88]	0.97 [0.94, 0.99]
Morton 1998a	63	10	6	684	0.91 [0.82, 0.97]	0.99 [0.97, 0.99]
Morton 1998b	28	14	3	522	0.90 [0.74, 0.98]	0.97 [0.96, 0.99]
Morton 1998c	22	11	6	630	0.79 [0.59, 0.92]	0.98 [0.97, 0.99]
Soyer 1995	61	17	4	77	0.94 [0.85, 0.98]	0.82 [0.73, 0.89]
Stanganelli 2000	37	21	18	3296	0.67 [0.53, 0.79]	0.99 [0.99, 1.00]
Steiner 1987	43	31	30	214	0.59 [0.47, 0.70]	0.87 [0.83, 0.91]
Thomas 1998	411	236	49	444	0.89 [0.86, 0.92]	0.65 [0.62, 0.69]
Unlu 2014	18	39	6	52	0.75 [0.53, 0.90]	0.57 [0.46, 0.67]
Walter 2012	17	152	1	603	0.94 [0.73, 1.00]	0.80 [0.77, 0.83]
Zaumseil 1983	312	76	25	6650	0.93 [0.89, 0.95]	0.99 [0.99, 0.99]

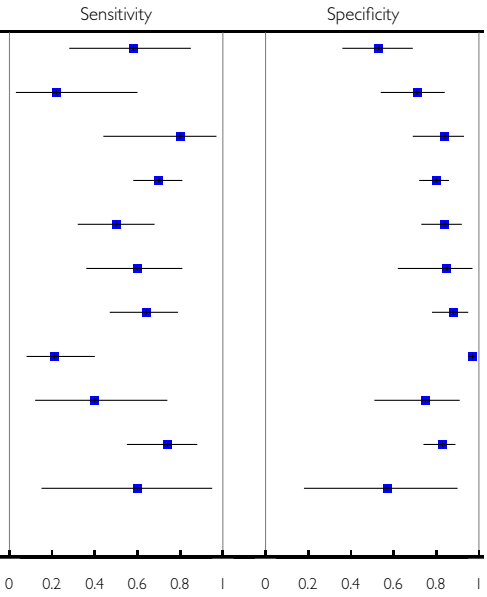


Test 4. Visual inspection - image-based (MEL).

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 4 Visual inspection - image-based (MEL)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Benelli 2001	7	18	5	20	0.58 [0.28, 0.85]	0.53 [0.36, 0.69]
Bourne 2012	2	12	7	29	0.22 [0.03, 0.60]	0.71 [0.54, 0.84]
Carli 2002b	8	7	2	36	0.80 [0.44, 0.97]	0.84 [0.69, 0.93]
Carli 2003a	45	27	19	109	0.70 [0.58, 0.81]	0.80 [0.72, 0.86]
de Giorgi 2012	17	11	17	58	0.50 [0.32, 0.68]	0.84 [0.73, 0.92]
Dolianitis 2005	12	3	8	17	0.60 [0.36, 0.81]	0.85 [0.62, 0.97]
Pizzichetta 2004	25	8	14	61	0.64 [0.47, 0.79]	0.88 [0.78, 0.95]
Rosendahl 2011	6	14	23	420	0.21 [0.08, 0.40]	0.97 [0.95, 0.98]
Stanganelli 1998a	4	5	6	15	0.40 [0.12, 0.74]	0.75 [0.51, 0.91]
Stanganelli 2005	23	18	8	85	0.74 [0.55, 0.88]	0.83 [0.74, 0.89]
Winkelmann 2016	3	3	2	4	0.60 [0.15, 0.95]	0.57 [0.18, 0.90]

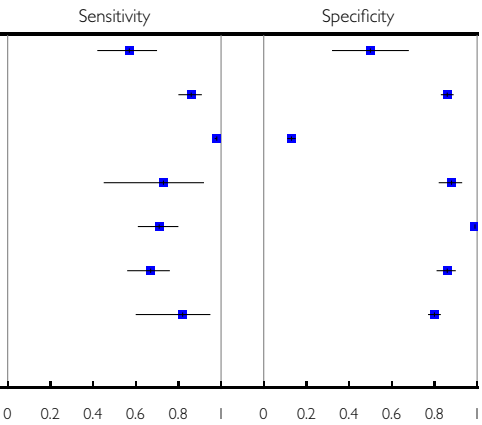


Test 5. Visual inspection - in-person (Any).

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 5 Visual inspection - in-person (Any)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Argenziano 2006	30	16	23	16	0.57 [0.42, 0.70]	0.50 [0.32, 0.68]
Chang 2013	131	84	21	533	0.86 [0.80, 0.91]	0.86 [0.83, 0.89]
Ek 2005	1711	722	43	106	0.98 [0.97, 0.98]	0.13 [0.11, 0.15]
McGovern 1992	11	21	4	156	0.73 [0.45, 0.92]	0.88 [0.82, 0.93]
Stanganelli 2000	70	29	28	3245	0.71 [0.61, 0.80]	0.99 [0.99, 0.99]
Steiner 1987	62	31	31	194	0.67 [0.56, 0.76]	0.86 [0.81, 0.90]
Walter 2012	18	152	4	599	0.82 [0.60, 0.95]	0.80 [0.77, 0.83]

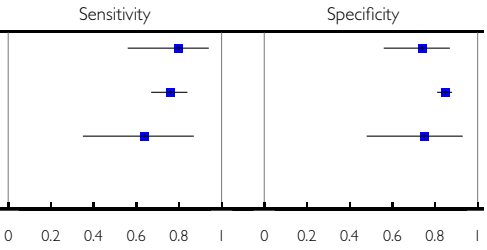


Test 6. Visual inspection - image-based (Any).

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 6 Visual inspection - image-based (Any)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Carli 2002b	16	9	4	25	0.80 [0.56, 0.94]	0.74 [0.56, 0.87]
Rosendahl 2011	79	54	25	305	0.76 [0.67, 0.84]	0.85 [0.81, 0.88]
Stanganelli 1998a	9	4	5	12	0.64 [0.35, 0.87]	0.75 [0.48, 0.93]

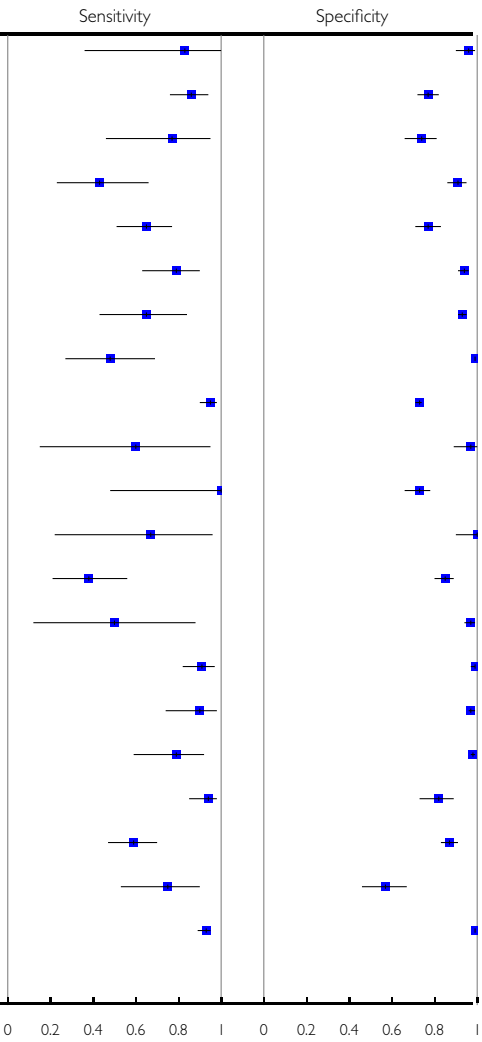


Test 7. MEL- VI - in-person - no algorithm.

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 7 MEL- VI - in-person - no algorithm

Study	TP	FP	FN	TN	Sensitivity	Specificity
Barzegari 2005	5	5	1	111	0.83 [0.36, 1.00]	0.96 [0.90, 0.99]
Bono 2002a	57	56	9	191	0.86 [0.76, 0.94]	0.77 [0.72, 0.82]
Bono 2002b	10	39	3	109	0.77 [0.46, 0.95]	0.74 [0.66, 0.81]
Bono 2006	10	16	13	167	0.43 [0.23, 0.66]	0.91 [0.86, 0.95]
Carli 2002a	35	46	19	156	0.65 [0.51, 0.77]	0.77 [0.71, 0.83]
Collas 1999	30	19	8	296	0.79 [0.63, 0.90]	0.94 [0.91, 0.96]
Dummer 1993	15	49	8	699	0.65 [0.43, 0.84]	0.93 [0.91, 0.95]
Ek 2005	11	23	12	2536	0.48 [0.27, 0.69]	0.99 [0.99, 0.99]
Gachon 2005	141	1058	8	2829	0.95 [0.90, 0.98]	0.73 [0.71, 0.74]
Green 1991	3	2	2	63	0.60 [0.15, 0.95]	0.97 [0.89, 1.00]
Grimaldi 2009	5	63	0	167	1.00 [0.48, 1.00]	0.73 [0.66, 0.78]
Langley 2001	4	0	2	34	0.67 [0.22, 0.96]	1.00 [0.90, 1.00]
Menzies 2009	12	46	20	253	0.38 [0.21, 0.56]	0.85 [0.80, 0.89]
Morales Callaghan 2008	3	5	3	189	0.50 [0.12, 0.88]	0.97 [0.94, 0.99]
Morton 1998a	63	10	6	684	0.91 [0.82, 0.97]	0.99 [0.97, 0.99]
Morton 1998b	28	14	3	522	0.90 [0.74, 0.98]	0.97 [0.96, 0.99]
Morton 1998c	22	11	6	630	0.79 [0.59, 0.92]	0.98 [0.97, 0.99]
Soyer 1995	61	17	4	77	0.94 [0.85, 0.98]	0.82 [0.73, 0.89]
Steiner 1987	43	31	30	214	0.59 [0.47, 0.70]	0.87 [0.83, 0.91]
Unlu 2014	18	39	6	52	0.75 [0.53, 0.90]	0.57 [0.46, 0.67]
Zaumseil 1983	312	76	25	6650	0.93 [0.89, 0.95]	0.99 [0.99, 0.99]

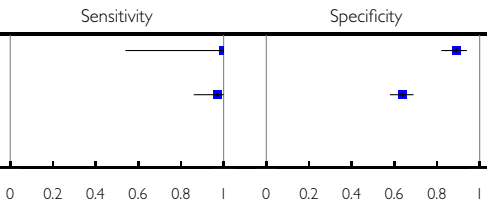


Test 8. MEL- VI - in-person - no algorithm (alternative thresholds).

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 8 MEL- VI - in-person - no algorithm (alternative thresholds)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Barzegari 2005	6	13	0	103	1.00 [0.54, 1.00]	0.89 [0.82, 0.94]
Collas 1999	37	114	1	201	0.97 [0.86, 1.00]	0.64 [0.58, 0.69]

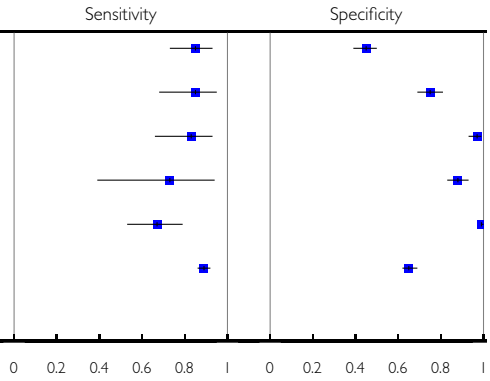


Test 9. MEL- VI - in-person - (A)BCD(E) at NR or standard threshold.

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 9 MEL- VI - in-person - (A)BCD(E) at NR or standard threshold

Study	TP	FP	FN	TN	Sensitivity	Specificity
Benelli 1999	51	189	9	152	0.85 [0.73, 0.93]	0.45 [0.39, 0.50]
Cristofolini 1994	28	46	5	141	0.85 [0.68, 0.95]	0.75 [0.69, 0.81]
Cristofolini 1997	29	4	6	137	0.83 [0.66, 0.93]	0.97 [0.93, 0.99]
McGovern 1992	8	21	3	160	0.73 [0.39, 0.94]	0.88 [0.83, 0.93]
Stanganelli 2000	37	21	18	3296	0.67 [0.53, 0.79]	0.99 [0.99, 1.00]
Thomas 1998	411	236	49	444	0.89 [0.86, 0.92]	0.65 [0.62, 0.69]

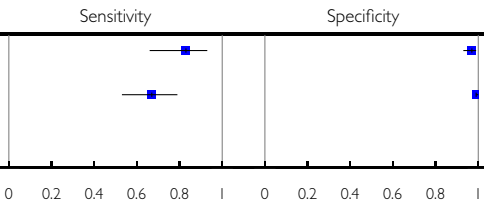


Test 10. MEL-VI - in-person - ABCD at NR.

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 10 MEL-VI - in-person - ABCD at NR

Study	TP	FP	FN	TN	Sensitivity	Specificity
Cristofolini 1997	29	4	6	137	0.83 [0.66, 0.93]	0.97 [0.93, 0.99]
Stanganelli 2000	37	21	18	3296	0.67 [0.53, 0.79]	0.99 [0.99, 1.00]

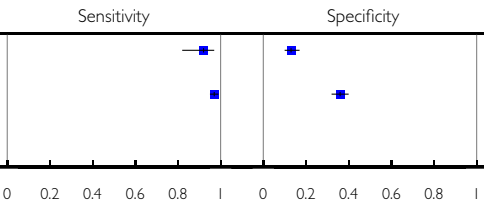


Test 11. MEL-VI - in-person - ABCDE at ≥ 1.

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 11 MEL-VI - in-person - ABCDE at ≥ 1

Study	TP	FP	FN	TN	Sensitivity	Specificity
Benelli 1999	55	297	5	44	0.92 [0.82, 0.97]	0.13 [0.10, 0.17]
Thomas 1998	448	435	12	245	0.97 [0.95, 0.99]	0.36 [0.32, 0.40]

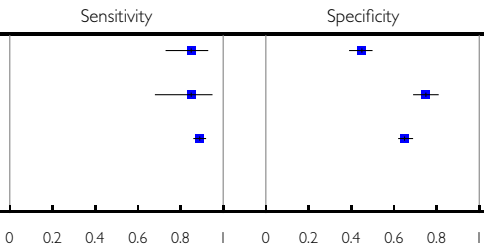


Test 12. MEL-VI - in-person - ABCDE at ≥ 2.

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 12 MEL-VI - in-person - ABCDE at ≥ 2

Study	TP	FP	FN	TN	Sensitivity	Specificity
Benelli 1999	51	189	9	152	0.85 [0.73, 0.93]	0.45 [0.39, 0.50]
Cristofolini 1994	28	46	5	141	0.85 [0.68, 0.95]	0.75 [0.69, 0.81]
Thomas 1998	411	236	49	444	0.89 [0.86, 0.92]	0.65 [0.62, 0.69]

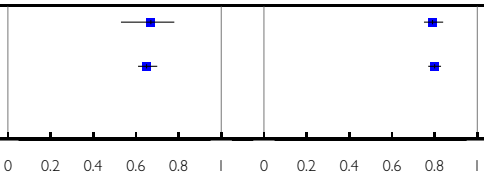


Test 13. MEL-VI - in-person - ABCDE at ≥ 3.

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 13 MEL-VI - in-person - ABCDE at ≥ 3

Study	TP	FP	FN	TN	Sensitivity	Specificity
Benelli 1999	40	70	20	271	0.67 [0.53, 0.78]	0.79 [0.75, 0.84]
Thomas 1998	301	136	159	544	0.65 [0.61, 0.70]	0.80 [0.77, 0.83]

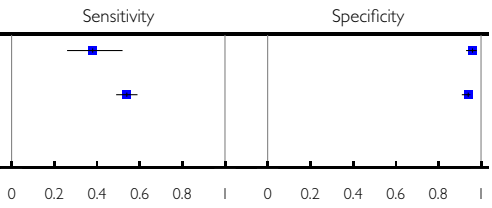


Test 14. MEL-VI - in-person - ABCDE at ≥ 4.

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 14 MEL-VI - in-person - ABCDE at ≥ 4

Study	TP	FP	FN	TN	Sensitivity	Specificity
Benelli 1999	23	15	37	326	0.38 [0.26, 0.52]	0.96 [0.93, 0.98]
Thomas 1998	248	44	212	636	0.54 [0.49, 0.59]	0.94 [0.91, 0.95]

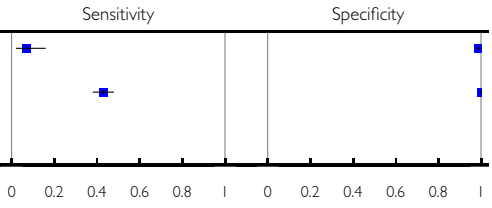


Test 15. MEL-VI - in-person - ABCDE at ≥ 5.

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 15 MEL-VI - in-person - ABCDE at ≥ 5

Study	TP	FP	FN	TN	Sensitivity	Specificity
Benelli 1999	4	2	56	339	0.07 [0.02, 0.16]	0.99 [0.98, 1.00]
Thomas 1998	198	3	262	677	0.43 [0.38, 0.48]	1.00 [0.99, 1.00]

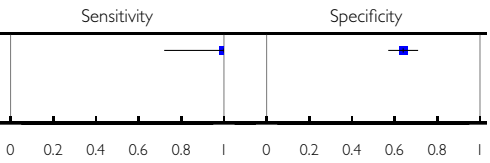


Test 16. MEL-VI - in-person - BCD at ≥ 1.

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 16 MEL-VI - in-person - BCD at ≥ 1

Study	TP	FP	FN	TN	Sensitivity	Specificity
McGovern 1992	11	65	0	116	1.00 [0.72, 1.00]	0.64 [0.57, 0.71]

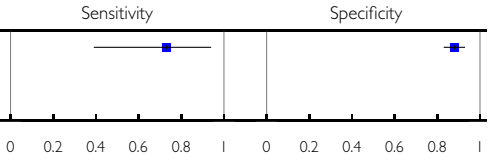


Test 17. MEL-VI - in-person - BCD at ≥ 2.

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 17 MEL-VI - in-person - BCD at ≥ 2

Study	TP	FP	FN	TN	Sensitivity	Specificity
McGovern 1992	8	21	3	160	0.73 [0.39, 0.94]	0.88 [0.83, 0.93]

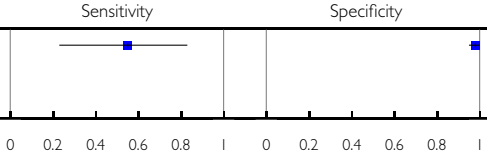


Test 18. MEL-VI - in-person - BCD at ≥ 3.

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 18 MEL-VI - in-person - BCD at ≥ 3

Study	TP	FP	FN	TN	Sensitivity	Specificity
McGovern 1992	6	3	5	178	0.55 [0.23, 0.83]	0.98 [0.95, 1.00]



Test 19. MEL-VI - in-person - 7point at ≥ 2.

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 19 MEL-VI - in-person - 7point at ≥ 2

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
McGovern 1992	11	64	1	129	0.92 [0.62, 1.00]	0.67 [0.60, 0.73]		

Test 20. MEL-VI - in-person - 7point at ≥ 3.

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 20 MEL-VI - in-person - 7point at ≥ 3

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
McGovern 1992	5	11	7	182	0.42 [0.15, 0.72]	0.94 [0.90, 0.97]		

Test 21. MEL-VI - in-person - 7point at ≥ 4.

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 21 MEL-VI - in-person - 7point at ≥ 4

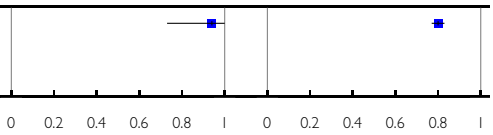
Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
McGovern 1992	3	2	9	191	0.25 [0.05, 0.57]	0.99 [0.96, 1.00]		

Test 22. MEL-VI - in-person - 7point(rev) at ≥ 3.

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 22 MEL-VI - in-person - 7point(rev) at ≥ 3

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Walter 2012	17	152	1	603	0.94 [0.73, 1.00]	0.80 [0.77, 0.83]		

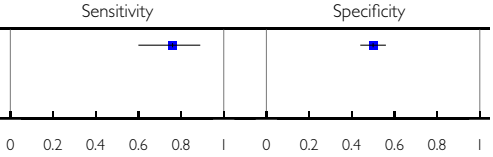


Test 23. MEL-VI - in-person - Collas at ≥ 1.

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 23 MEL-VI - in-person - Collas at ≥ 1

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Collas 1999	29	157	9	158	0.76 [0.60, 0.89]	0.50 [0.44, 0.56]		

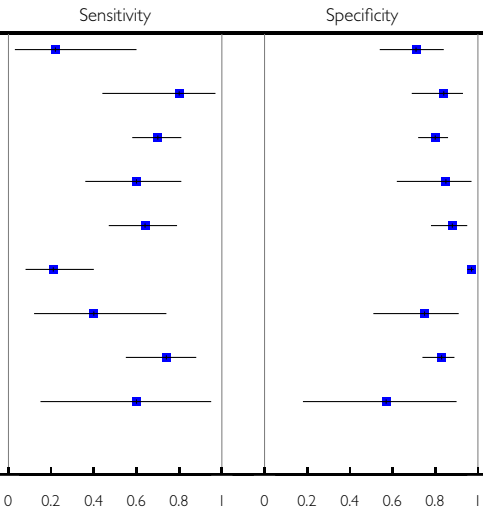


Test 24. MEL- VI - image-based - no algorithm.

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 24 MEL- VI - image-based - no algorithm

Study	TP	FP	FN	TN	Sensitivity	Specificity
Bourne 2012	2	12	7	29	0.22 [0.03, 0.60]	0.71 [0.54, 0.84]
Carli 2002b	8	7	2	36	0.80 [0.44, 0.97]	0.84 [0.69, 0.93]
Carli 2003a	45	27	19	109	0.70 [0.58, 0.81]	0.80 [0.72, 0.86]
Dolianitis 2005	12	3	8	17	0.60 [0.36, 0.81]	0.85 [0.62, 0.97]
Pizzichetta 2004	25	8	14	61	0.64 [0.47, 0.79]	0.88 [0.78, 0.95]
Rosendahl 2011	6	14	23	420	0.21 [0.08, 0.40]	0.97 [0.95, 0.98]
Stanganelli 1998a	4	5	6	15	0.40 [0.12, 0.74]	0.75 [0.51, 0.91]
Stanganelli 2005	23	18	8	85	0.74 [0.55, 0.88]	0.83 [0.74, 0.89]
Winkelmann 2016	3	3	2	4	0.60 [0.15, 0.95]	0.57 [0.18, 0.90]

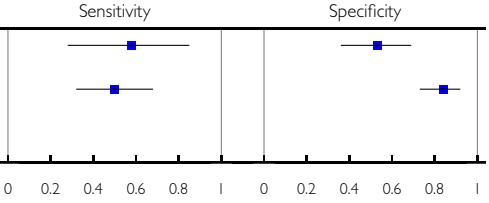


Test 26. MEL-VI - image-based - ABCD(E) at standard.

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 26 MEL-VI - image-based - ABCD(E) at standard

Study	TP	FP	FN	TN	Sensitivity	Specificity
Benelli 2001	7	18	5	20	0.58 [0.28, 0.85]	0.53 [0.36, 0.69]
de Giorgi 2012	17	11	17	58	0.50 [0.32, 0.68]	0.84 [0.73, 0.92]



Test 27. MEL-VI - image-based - ABCD at ≥ 2.

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 27 MEL-VI - image-based - ABCD at ≥ 2

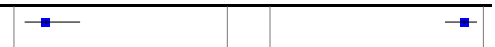
Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
de Giorgi 2012	17	11	17	58	0.50 [0.32, 0.68]	0.84 [0.73, 0.92]		

Test 28. MEL-VI - image-based - ABCD at ≥ 3.

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 28 MEL-VI - image-based - ABCD at ≥ 3

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
de Giorgi 2012	5	6	29	63	0.15 [0.05, 0.31]	0.91 [0.82, 0.97]		

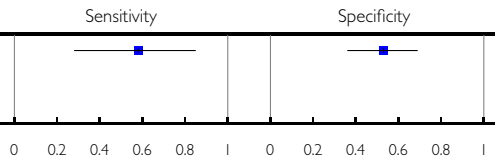


Test 29. MEL-VI - image-based - ABCDE at ≥ 2.

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 29 MEL-VI - image-based - ABCDE at ≥ 2

Study	TP	FP	FN	TN	Sensitivity	Specificity
Benelli 2001	7	18	5	20	0.58 [0.28, 0.85]	0.53 [0.36, 0.69]

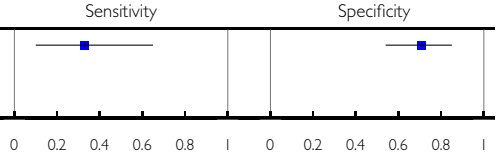


Test 30. MEL-VI - image-based - ABCDE at ≥ 3.

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 30 MEL-VI - image-based - ABCDE at ≥ 3

Study	TP	FP	FN	TN	Sensitivity	Specificity
Benelli 2001	4	11	8	27	0.33 [0.10, 0.65]	0.71 [0.54, 0.85]

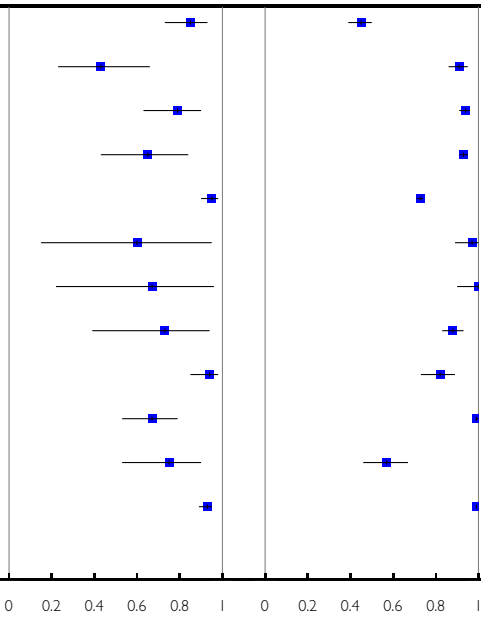


Test 31. MEL- VI - in-person - experience NR.

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 31 MEL- VI - in-person - experience NR

Study	TP	FP	FN	TN	Sensitivity	Specificity
Benelli 1999	51	189	9	152	0.85 [0.73, 0.93]	0.45 [0.39, 0.50]
Bono 2006	10	16	13	167	0.43 [0.23, 0.66]	0.91 [0.86, 0.95]
Collas 1999	30	19	8	296	0.79 [0.63, 0.90]	0.94 [0.91, 0.96]
Dummer 1993	15	49	8	699	0.65 [0.43, 0.84]	0.93 [0.91, 0.95]
Gachon 2005	141	1058	8	2829	0.95 [0.90, 0.98]	0.73 [0.71, 0.74]
Green 1991	3	2	2	63	0.60 [0.15, 0.95]	0.97 [0.89, 1.00]
Langley 2001	4	0	2	34	0.67 [0.22, 0.96]	1.00 [0.90, 1.00]
McGovern 1992	8	21	3	160	0.73 [0.39, 0.94]	0.88 [0.83, 0.93]
Soyer 1995	61	17	4	77	0.94 [0.85, 0.98]	0.82 [0.73, 0.89]
Stanganelli 2000	37	21	18	3296	0.67 [0.53, 0.79]	0.99 [0.99, 1.00]
Unlu 2014	18	39	6	52	0.75 [0.53, 0.90]	0.57 [0.46, 0.67]
Zaumseil 1983	312	76	25	6650	0.93 [0.89, 0.95]	0.99 [0.99, 0.99]

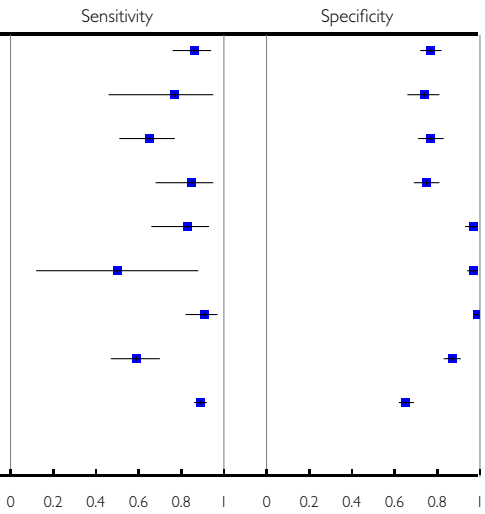


Test 32. MEL- VI - in-person - experience high.

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 32 MEL- VI - in-person - experience high

Study	TP	FP	FN	TN	Sensitivity	Specificity
Bono 2002a	57	56	9	191	0.86 [0.76, 0.94]	0.77 [0.72, 0.82]
Bono 2002b	10	39	3	109	0.77 [0.46, 0.95]	0.74 [0.66, 0.81]
Carli 2002a	35	46	19	156	0.65 [0.51, 0.77]	0.77 [0.71, 0.83]
Cristofolini 1994	28	46	5	141	0.85 [0.68, 0.95]	0.75 [0.69, 0.81]
Cristofolini 1997	29	4	6	137	0.83 [0.66, 0.93]	0.97 [0.93, 0.99]
Morales Callaghan 2008	3	5	3	189	0.50 [0.12, 0.88]	0.97 [0.94, 0.99]
Morton 1998a	63	10	6	684	0.91 [0.82, 0.97]	0.99 [0.97, 0.99]
Steiner 1987	43	31	30	214	0.59 [0.47, 0.70]	0.87 [0.83, 0.91]
Thomas 1998	411	236	49	444	0.89 [0.86, 0.92]	0.65 [0.62, 0.69]

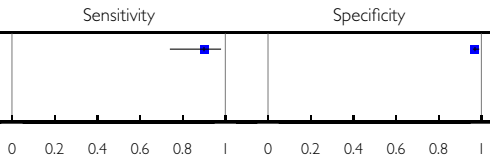


Test 33. MEL- VI - in-person - experience moderate.

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 33 MEL- VI - in-person - experience moderate

Study	TP	FP	FN	TN	Sensitivity	Specificity
Morton 1998b	28	14	3	522	0.90 [0.74, 0.98]	0.97 [0.96, 0.99]

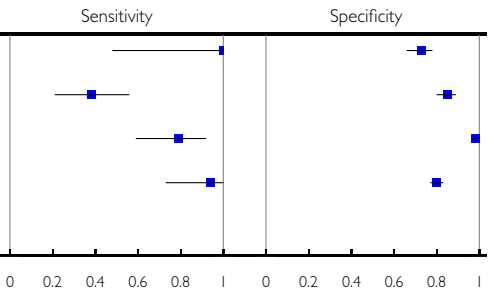


Test 34. MEL- VI - in-person - experience low.

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 34 MEL- VI - in-person - experience low

Study	TP	FP	FN	TN	Sensitivity	Specificity
Grimaldi 2009	5	63	0	167	1.00 [0.48, 1.00]	0.73 [0.66, 0.78]
Menzies 2009	12	46	20	253	0.38 [0.21, 0.56]	0.85 [0.80, 0.89]
Morton 1998c	22	11	6	630	0.79 [0.59, 0.92]	0.98 [0.97, 0.99]
Walter 2012	17	152	1	603	0.94 [0.73, 1.00]	0.80 [0.77, 0.83]

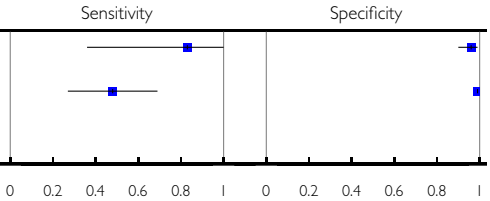


Test 35. MEL- VI - in-person - experience mixed.

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 35 MEL- VI - in-person - experience mixed

Study	TP	FP	FN	TN	Sensitivity	Specificity
Barzegari 2005	5	5	1	111	0.83 [0.36, 1.00]	0.96 [0.90, 0.99]
Ek 2005	11	23	12	2536	0.48 [0.27, 0.69]	0.99 [0.99, 0.99]

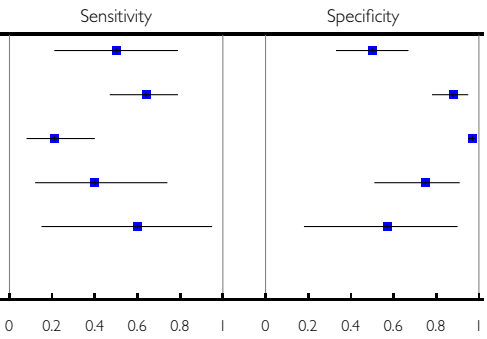


Test 36. MEL- VI - image-based - experience NR.

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 36 MEL- VI - image-based - experience NR

Study	TP	FP	FN	TN	Sensitivity	Specificity
Benelli 2001	6	19	6	19	0.50 [0.21, 0.79]	0.50 [0.33, 0.67]
Pizzichetta 2004	25	8	14	61	0.64 [0.47, 0.79]	0.88 [0.78, 0.95]
Rosendahl 2011	6	14	23	420	0.21 [0.08, 0.40]	0.97 [0.95, 0.98]
Stanganelli 1998a	4	5	6	15	0.40 [0.12, 0.74]	0.75 [0.51, 0.91]
Winkelmann 2016	3	3	2	4	0.60 [0.15, 0.95]	0.57 [0.18, 0.90]

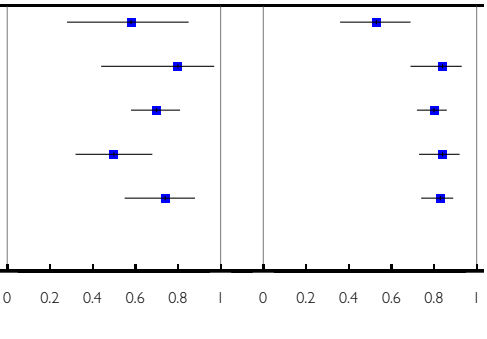


Test 37. MEL- VI - image-based - experience high.

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 37 MEL- VI - image-based - experience high

Study	TP	FP	FN	TN	Sensitivity	Specificity
Benelli 2001	7	18	5	20	0.58 [0.28, 0.85]	0.53 [0.36, 0.69]
Carli 2002b	8	7	2	36	0.80 [0.44, 0.97]	0.84 [0.69, 0.93]
Carli 2003a	45	27	19	109	0.70 [0.58, 0.81]	0.80 [0.72, 0.86]
de Giorgi 2012	17	11	17	58	0.50 [0.32, 0.68]	0.84 [0.73, 0.92]
Stanganelli 2005	23	18	8	85	0.74 [0.55, 0.88]	0.83 [0.74, 0.89]

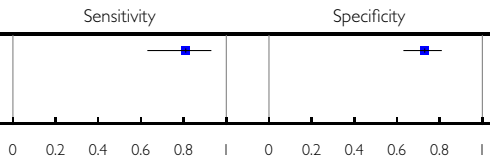


Test 38. MEL- VI - image-based - experience low.

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 38 MEL- VI - image-based - experience low

Study	TP	FP	FN	TN	Sensitivity	Specificity
Stanganelli 2005	25	28	6	75	0.81 [0.63, 0.93]	0.73 [0.63, 0.81]

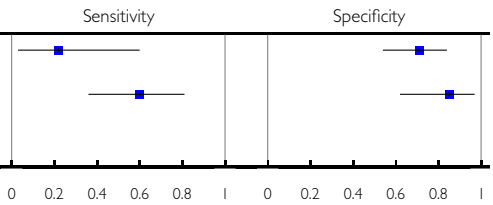


Test 39. MEL- VI - image-based - experience mixed.

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 39 MEL- VI - image-based - experience mixed

Study	TP	FP	FN	TN	Sensitivity	Specificity
Bourne 2012	2	12	7	29	0.22 [0.03, 0.60]	0.71 [0.54, 0.84]
Dolianitis 2005	12	3	8	17	0.60 [0.36, 0.81]	0.85 [0.62, 0.97]

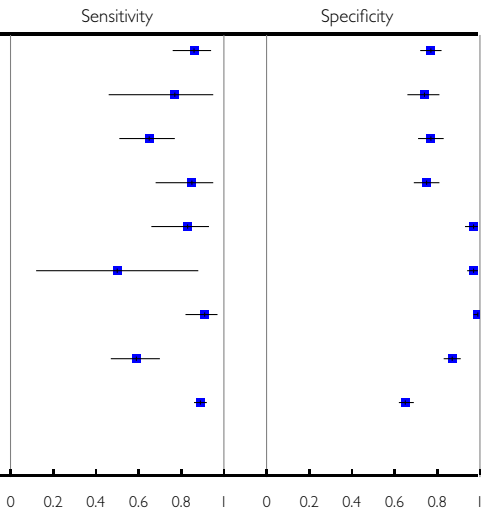


Test 40. VI - in-person - expert consultant (MEL).

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 40 VI - in-person - expert consultant (MEL)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Bono 2002a	57	56	9	191	0.86 [0.76, 0.94]	0.77 [0.72, 0.82]
Bono 2002b	10	39	3	109	0.77 [0.46, 0.95]	0.74 [0.66, 0.81]
Carli 2002a	35	46	19	156	0.65 [0.51, 0.77]	0.77 [0.71, 0.83]
Cristofolini 1994	28	46	5	141	0.85 [0.68, 0.95]	0.75 [0.69, 0.81]
Cristofolini 1997	29	4	6	137	0.83 [0.66, 0.93]	0.97 [0.93, 0.99]
Morales Callaghan 2008	3	5	3	189	0.50 [0.12, 0.88]	0.97 [0.94, 0.99]
Morton 1998a	63	10	6	684	0.91 [0.82, 0.97]	0.99 [0.97, 0.99]
Steiner 1987	43	31	30	214	0.59 [0.47, 0.70]	0.87 [0.83, 0.91]
Thomas 1998	411	236	49	444	0.89 [0.86, 0.92]	0.65 [0.62, 0.69]

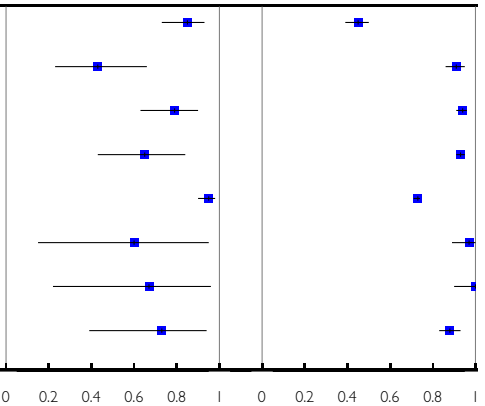


Test 41. VI - in-person - consultant (MEL).

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 41 VI - in-person - consultant (MEL)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Benelli 1999	51	189	9	152	0.85 [0.73, 0.93]	0.45 [0.39, 0.50]
Bono 2006	10	16	13	167	0.43 [0.23, 0.66]	0.91 [0.86, 0.95]
Collas 1999	30	19	8	296	0.79 [0.63, 0.90]	0.94 [0.91, 0.96]
Dummer 1993	15	49	8	699	0.65 [0.43, 0.84]	0.93 [0.91, 0.95]
Gachon 2005	141	1058	8	2829	0.95 [0.90, 0.98]	0.73 [0.71, 0.74]
Green 1991	3	2	2	63	0.60 [0.15, 0.95]	0.97 [0.89, 1.00]
Langley 2001	4	0	2	34	0.67 [0.22, 0.96]	1.00 [0.90, 1.00]
McGovern 1992	8	21	3	160	0.73 [0.39, 0.94]	0.88 [0.83, 0.93]



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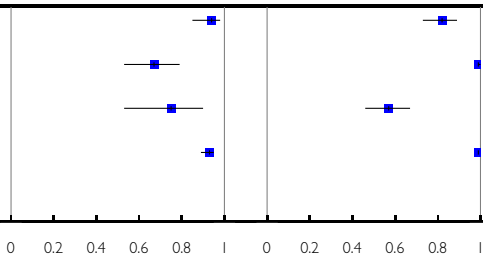
Study	TP	FP	FN	TN	Sensitivity	Specificity
Soyer 1995	61	17	4	77	0.94 [0.85, 0.98]	0.82 [0.73, 0.89]
Stanganelli 2000	37	21	18	3296	0.67 [0.53, 0.79]	0.99 [0.99, 1.00]
Unlu 2014	18	39	6	52	0.75 [0.53, 0.90]	0.57 [0.46, 0.67]
Zaumseil 1983	312	76	25	6650	0.93 [0.89, 0.95]	0.99 [0.99, 0.99]

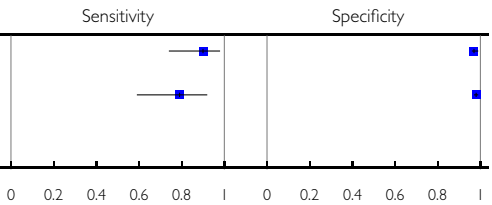


Test 42. VI - in-person - resident/registrar (MEL).

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 42 VI - in-person - resident/registrar (MEL)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Morton 1998b	28	14	3	522	0.90 [0.74, 0.98]	0.97 [0.96, 0.99]
Morton 1998c	22	11	6	630	0.79 [0.59, 0.92]	0.98 [0.97, 0.99]

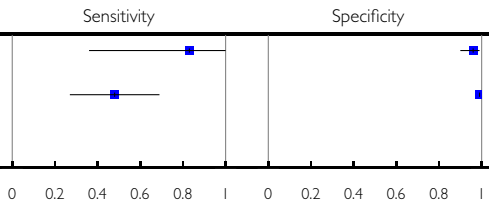


Test 43. VI - in-person - mixed qualifications (secondary care) (MEL).

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 43 VI - in-person - mixed qualifications (secondary care) (MEL)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Barzegari 2005	5	5	1	111	0.83 [0.36, 1.00]	0.96 [0.90, 0.99]
Ek 2005	11	23	12	2536	0.48 [0.27, 0.69]	0.99 [0.99, 0.99]

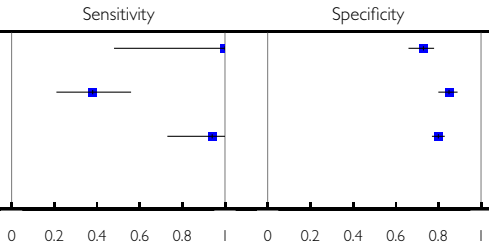


Test 44. VI - in-person - GP (MEL).

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 44 VI - in-person - GP (MEL)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Grimaldi 2009	5	63	0	167	1.00 [0.48, 1.00]	0.73 [0.66, 0.78]
Menzies 2009	12	46	20	253	0.38 [0.21, 0.56]	0.85 [0.80, 0.89]
Walter 2012	17	152	1	603	0.94 [0.73, 1.00]	0.80 [0.77, 0.83]

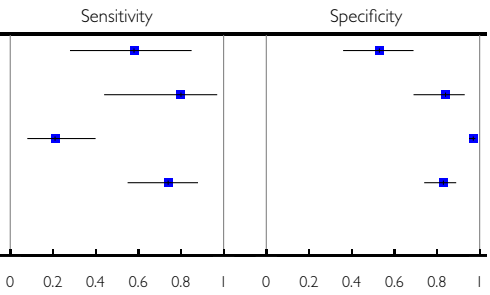


Test 45. MEL- VI - image-based - expert consultant.

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 45 MEL- VI - image-based - expert consultant

Study	TP	FP	FN	TN	Sensitivity	Specificity
Benelli 2001	7	18	5	20	0.58 [0.28, 0.85]	0.53 [0.36, 0.69]
Carli 2002b	8	7	2	36	0.80 [0.44, 0.97]	0.84 [0.69, 0.93]
Rosendahl 2011	6	14	23	420	0.21 [0.08, 0.40]	0.97 [0.95, 0.98]
Stanganelli 2005	23	18	8	85	0.74 [0.55, 0.88]	0.83 [0.74, 0.89]

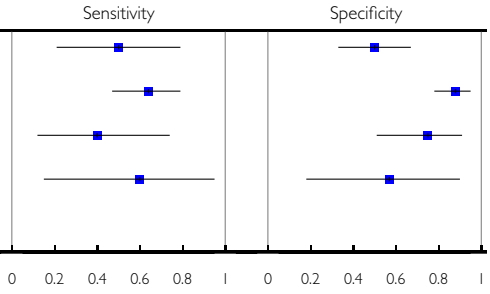


Test 46. MEL- VI - image-based - consultant.

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 46 MEL- VI - image-based - consultant

Study	TP	FP	FN	TN	Sensitivity	Specificity
Benelli 2001	6	19	6	19	0.50 [0.21, 0.79]	0.50 [0.33, 0.67]
Pizzichetta 2004	25	8	14	61	0.64 [0.47, 0.79]	0.88 [0.78, 0.95]
Stanganelli 1998a	4	5	6	15	0.40 [0.12, 0.74]	0.75 [0.51, 0.91]
Winkelmann 2016	3	3	2	4	0.60 [0.15, 0.95]	0.57 [0.18, 0.90]

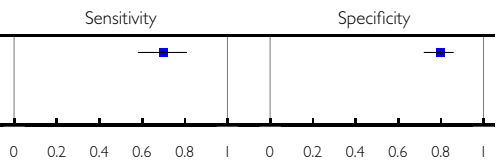


Test 47. MEL- VI - image-based - mixed qualifications (secondary care).

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 47 MEL- VI - image-based - mixed qualifications (secondary care)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Carli 2003a	45	27	19	109	0.70 [0.58, 0.81]	0.80 [0.72, 0.86]

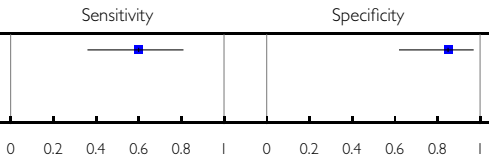


Test 48. MEL- VI - image-based - mixed qualifications (secondary/primary care).

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 48 MEL- VI - image-based - mixed qualifications (secondary/primary care)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Dolianitis 2005	12	3	8	17	0.60 [0.36, 0.81]	0.85 [0.62, 0.97]

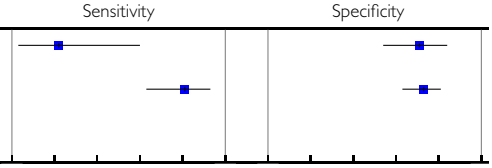


Test 49. MEL- VI - image-based - mixed qualifications (primary care).

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 49 MEL- VI - image-based - mixed qualifications (primary care)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Bourne 2012	2	12	7	29	0.22 [0.03, 0.60]	0.71 [0.54, 0.84]
Stanganelli 2005	25	28	6	75	0.81 [0.63, 0.93]	0.73 [0.63, 0.81]

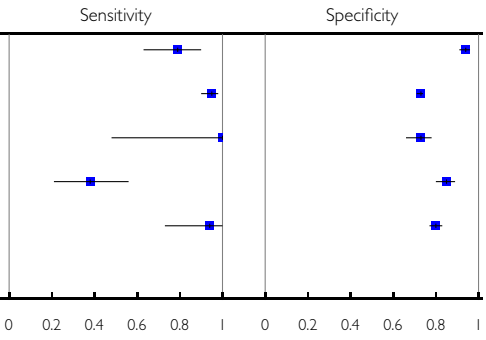


Test 51. MEL - Selected on quality - pathway 2 or 3.

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 51 MEL - Selected on quality - pathway 2 or 3

Study	TP	FP	FN	TN	Sensitivity	Specificity
Collas 1999	30	19	8	296	0.79 [0.63, 0.90]	0.94 [0.91, 0.96]
Gachon 2005	141	1058	8	2829	0.95 [0.90, 0.98]	0.73 [0.71, 0.74]
Grimaldi 2009	5	63	0	167	1.00 [0.48, 1.00]	0.73 [0.66, 0.78]
Menzies 2009	12	46	20	253	0.38 [0.21, 0.56]	0.85 [0.80, 0.89]
Walter 2012	17	152	1	603	0.94 [0.73, 1.00]	0.80 [0.77, 0.83]

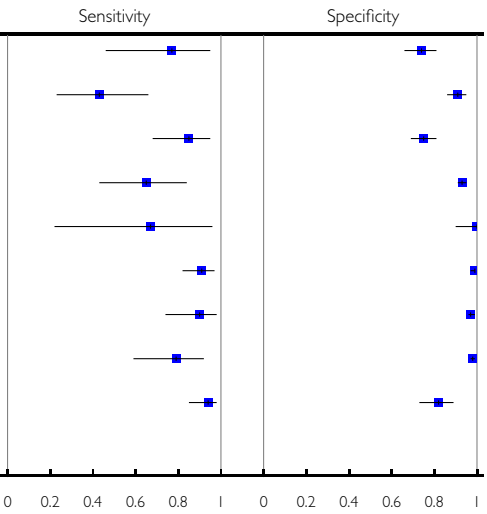


Test 52. MEL - Selected on quality - pathway 5.

Review: Visual inspection for diagnosing cutaneous melanoma in adults

Test: 52 MEL - Selected on quality - pathway 5

Study	TP	FP	FN	TN	Sensitivity	Specificity
Bono 2002b	10	39	3	109	0.77 [0.46, 0.95]	0.74 [0.66, 0.81]
Bono 2006	10	16	13	167	0.43 [0.23, 0.66]	0.91 [0.86, 0.95]
Cristofolini 1994	28	46	5	141	0.85 [0.68, 0.95]	0.75 [0.69, 0.81]
Dummer 1993	15	49	8	699	0.65 [0.43, 0.84]	0.93 [0.91, 0.95]
Langley 2001	4	0	2	34	0.67 [0.22, 0.96]	1.00 [0.90, 1.00]
Morton 1998a	63	10	6	684	0.91 [0.82, 0.97]	0.99 [0.97, 0.99]
Morton 1998b	28	14	3	522	0.90 [0.74, 0.98]	0.97 [0.96, 0.99]
Morton 1998c	22	11	6	630	0.79 [0.59, 0.92]	0.98 [0.97, 0.99]
Soyer 1995	61	17	4	77	0.94 [0.85, 0.98]	0.82 [0.73, 0.89]



ADDITIONAL TABLES

Table 1. Primary analyses for detection of invasive melanoma or atypical intraepidermal melanocytic variants by position on the clinical pathway

In-person evaluations (n = 28)						
Position on pathway	**Datasets**	**Lesions (melanomas)**	**Sensitivity % (95% CI %)**	**Variance**	**Specificity % (95% CI %)**	**Variance**
Participants with limited prior testing (unselected on reference standard)						
Clear	**3**	**1339 (55)**	**92.4 (26.2 to 99.8)**	**6.26**	**79.7 (73.7 to 84.7)**	**0.07**
Participants with limited prior testing (selected for excision)						
Clear	**2[a]**	**4228 (160)**	**90.1 (70.0 to 97.3)**	**0.53**	**81.3 (67.5 to 90.0)**	**0.25**
Unclear	1	353 (38)	78.9 (62.7 to 90.4)	-	94.0 (90.7 to 96.3)	-

Table 1. Primary analyses for detection of invasive melanoma or atypical intraepidermal melanocytic variants by position on the clinical pathway (*Continued*)

Combined	3	4581 (198)	87.2 (73.2 to 94.4)	0.45	87.1 (74.6 to 94.0)	0.51
Referred participants (unselected on reference standard)						
Clear	**2**	**3494 (61)**	**74.6 (48.9 to 90.0)**	**0.14**	**98.6 (94.7 to 99.6)**	**0.77**
Referred participants (selected for excision)						
Clear	**8**	**5331 (258)**	**76.7 (61.7 to 87.1)**	**0.78**	**95.7 (89.7 to 98.3)**	**1.73**
Unclear	9	9611 (1015)	82.8 (74.4 to 88.9)	0.34	89.2 (71.1 to 96.5)	3.21
Combined	17	14942 (1273)	79.7 (71.7 to 85.8)	0.59	93.0 (85.4 to 96.8)	2.59
Referred participants with equivocal lesions (selected for excision)						
Clear	**2**[a]	**930 (88)**	**84.7 (55.5 to 96.1)**	**0.93**	**89.5 (79.5 to 95.0)**	**0.27**
Unclear	1	318 (73)	61.4 (49.0 to 72.9)	-	87.3 (82.5 to 91.2)	-
Combined	3	1248 (161)	76.4 (48.4 to 91.8)	1.03	88.8 (81.8 to 93.3)	0.21
b. Image-based evaluations (n = 11)						
Position on pathway	**Datasets**	**Lesions (melanomas)**	**Sensitivity (95% CI %)**	**Variance**	**Specificity (95% CI %)**	**Variance**
Participants with limited prior testing (selected for excision)						
Clear	**1**	**50 (9)**	**22.2 (2.8 to 60.0)**	-	**70.7 (54.4 to 83.9)**	-
Unclear	1	463 (29)	20.7 (8.0 to 39.7)	-	96.8 (94.6 to 98.2)	-
Combined	2	513 (38)	21.4 (10.0 to 40.1)	0	90.9 (60.7 to 98.1)	1.50
Referred participants (unselected on reference standard)						

Table 1. Primary analyses for detection of invasive melanoma or atypical intraepidermal melanocytic variants by position on the clinical pathway (*Continued*)

Clear	**1**	**134 (31)**	**74.2 (55.4 to 88.1)**	-	**82.5 (73.8 to 89.3)**	**1**
Referred participants (selected for excision)						
Unclear	6	293 (96)	60.3 (49.2 to 70.5)	0.02	77.0 (63.9 to 86.4)	0.40
Referred participants with equivocal lesions (selected for excision)						
Unclear	2	303 (98)	61.9 (46.7 to 75.0)	0.10	81.8 (75.2 to 87.0)	0.01

CI: confidence interval

[a] Sensitivity and specificity estimated independently in separate models due to sparse data.

Table 2. Secondary analyses for primary target condition by covariate

Subgroup	Datasets	Lesions (melanomas)	Diagnostic odds ratio (DOR) (95% CI)	Relative DOR (95% CI)	P value (DOR)	P value[a] (hierarchical summary receiver-operator curves (HSROC) models)
Differences: in-person and image based evaluations						
In-person	28	25,604 (1748)	37.5 (21.7 to 64.7)	8.54 (2.89 to 25.3)	< 0.001	0.001
Image-based	11	1243 (263)	4.38 (1.79 to 10.8)	-	-	-
Analyses based on in-person evaluations only (n = 28)						
Study setting						
Primary/community/private	6	5920 (253)	27.6 (6.95 to 109)	-	-	-
Secondary	10	10,419 (1019)	39.0 (13.8 to 110)	-	-	-
Specialist clinic	12	9265 (476)	44.4 (17.2 to 115)	Secondary/specialist vs primary[b]: 1.51 (0.32 to 7.09)	0.59	0.62

Table 2. Secondary analyses for primary target condition by covariate (*Continued*)

Use of a diagnostic algorithm						
No algorithm used	21	19,330 (1076)	37.3 (18.0 to 77.3)	-	-	-
Any algorithm used	7	6274 (672)	38.5 (11.3 to 132)	1.03 (0.25 to 4.34)	0.96	0.55
Type of reference standard used						
Histology alone	22	20,783 (1627)	39.1 (19.7 to 77.8)	-	-	-
Histology plus any other	6	4821 (121)	29.7 (6.60 to 134)	0.76 (0.14 to 4.02)	0.74	0.68
Prevalence						
Prevalence ≤ 0.1	16	21,907 (811)	63.7 (28.6 to 142)	-	-	-
Prevalence > 0.1	12	3697 (937)	19.6 (8.39 to 45.8)	0.31 (0.09 to 1.00)	0.05	0.06

CI: confidence interval; **DOR**: diagnostic odds ratio; **RDOR**: relative diagnostic odds ratio

[a] Likelihood ratio test assessing differences in both accuracy and threshold.
[b] Secondary vs primary 1.41 (0.25 to 7.93), P = 0.68; specialist vs primary 1.61 (0.30 to 8.63), P = 0.56; specialist vs secondary 1.14 (0.28 to 4.68), P = 0.85.

Table 3. Visual inspection for detection of melanoma and atypical intraepidermal melanocytic variants - by algorithm

Test (threshold)	Datasets	Lesions (melanomas)	Pooled sensitivity (95% CI %)	Pooled specificity (95% CI %)	Diagnostic odds ratio (DOR) (95% CI)
In-person evaluations					
No algorithm	21	19,330 (1076)	78% (68 to 85)	93% (88 to 96)	46.2 (21.9 to 97.5)
(A)BCD(E)[a]	6[b]	5501 (654)	83% (75 to 88)	88% (64 to 97)	36.6 (7.94 to 168)
7-point checklist at ≥ 2	1	205 (12)	92% (62 to 1.00)	65% (58 to 72)	22.8 (2.08 to 176)
7-point checklist at ≥ 3	1	205 (12)	42% (15 to 72)	93% (89 to 96)	11.8 (3.22 to 43.3)

Table 3. Visual inspection for detection of melanoma and atypical intraepidermal melanocytic variants - by algorithm (*Continued)*

7-point checklist at ≥ 4	1	205 (12)	25% (07 to 57)	98% (96 to 100)	31.8 (4.71 to 215)
7-point checklist (revised) at ≥ 3	1	773 (18)	94% (73 to 100)	80% (77 to 83)	-
Collas algorithm at ≥ 1	1	353 (38)	76% (60 to 89)	50% (44 to 56)	3.24 (1.49 to 7.07)
Image-based evaluations					
No algorithm	9	1090 (217)	58% (43 to 71)	84% (76 to 90)	7.47 (4.12 to 13.5)
ABCD(E)[d]	2	153 (46)	53% (37 to 70)	71% (45 to 88)	2.87 (0.93 to 8.79)

CI: confidence interval

[a] Combines data from studies using ABCD with threshold not reported (n = 2), ABCDE with at least 2 characteristics present (n = 3) and BCD with at least 2 characteristics present (n = 1).

[b] Due to non-convergence, the bivariate models were fitted assuming zero correlation between the logit sensitivity and logit specificity and removing the random-effects term for specificity when estimating sensitivity and the random-effects term for sensitivity when estimating specificity.

[c] Study authors developed and used own algorithm.

[d] Combines data from studies using ABCD with at least 2 characteristics present (n = 1) and ABCDE with at least 2 characteristics present (n = 1).

Table 4. Secondary analyses for detection of melanoma and atypical intraepidermal melanocytic variants by observer

Subgroup	Datasets	Lesions (melanomas)	Diagnostic odds ratio (DOR) (95% CI)	Relative DOR (RDOR) (95% CI)	P value (for RDOR)	P value[a] (hierarchical summary receiver-operator curves (HSROC) models)
In-person evaluations						
Expert consultant	9	3547	29.0 (11.0 to 76.2)	1	-	0.36
Consultant	13	16,858	38.4 (16.9 to 87.6)	1.32 (0.37 to 4.71)	0.65	-
Resident/ registrar	2	1339	12.9 (1.99 to 84.0)	0.45 (0.05 to 3.67)	0.44	-
Mixed (secondary care)	2	2704	48.0 (4.54 to 507)	1.65 (0.13 to 21.4)	0.69	-

Table 4. Secondary analyses for detection of melanoma and atypical intraepidermal melanocytic variants by observer (*Continued*)

GP	3	1236	211 (24.9 to 1788)	7.28 (0.69 to 76.3)	0.09	-
Image-based evaluations						
Expert consultant	6	974	20.5 (4.82 to 86.9)	1	-	0.22
Consultant	4	200	3.76 (1.15 to 12.3)	0.18 (0.04 to 0.90)	0.04	-
Mixed (secondary care)	1	200	10.9 (2.02 to 59.2)	0.53 (0.07 to 3.97)	0.50	-
Mixed (secondary/primary care)	1	40	11.5 (0.94 to 142)	0.56 (0.04 to 7.51)	0.63	-
Mixed (primary care)	2	184	6.60 (1.73 to 25.2)	0.32 (0.07 to 1.40)	0.11	-

CI: confidence interval; **DOR**: diagnostic odds ratio; **RDOR**: relative diagnostic odds ratio

[a] Likelihood ratio test assessing differences in both accuracy and threshold.

Table 5. Results for studies reporting data for more than one observer

Study Algorithm (diagnostic approach) Dis/non-dis; prevalence	Observer qualification	Sensitivity (95% CI %)	Specificity (95% CI %)	Observer qualification	Sensitivity (95% CI %)	Specificity (95% CI %)	Observer qualification	Sensitivity (95% CI %)	Specificity (95% CI %)
Target condition: invasive melanoma and/or atypical intraepidermalmelanocytic variants									
Benelli 2001 ABCDE (i-b) 12/38; 24%	-	-	-	Dermatologist (n = 65)	50% (21 to 79)	50% (33 to 67)	Expert dermatologists (n = 1)	58% (28 to 85)	53% (36 to 69)

Table 5. Results for studies reporting data for more than one observer (*Continued*)

Morton 1998a; Morton 1998b; Morton 1998c No algorithm (in-p) Different lesions per obs	Registrar (n = 6) 69/694; 9%	79% (59 to 92)	98% (97 to 99)	Senior registrar (n = 2) 31/536; 5%	90% (74 to 98)	97% (96 to 99)	Expert dermatologists (n = 2) 28/641; 4%	91% (82 to 97)	99% (97 to 99)
Stanganelli 2005 No algorithm (i-b) 31/103; 23%	GP (n = 3)	81% (63 to 93)	73% (63 to 81)	-	-	-	Experienced dermatologists (n = 3)	74% (55 to 88)	83% (74 to 89)
Target condition: invasive melanoma alone									
Lorentzen 1999 No algorithm (i-b) 49/183; 21%	-	-	-	Non-expert dermatology residents (n = 5)	61% (46 to 75)	88% (82 to 92)	Experienced dermatologists (n = 4)	78% (63 to 88)	89% (84 to 93)
Rao 1997 ABCD (i-b) 21/51; 29%	-	-	-	Melanoma Fellow 1 (n = 1)	90% (70 to 99)	80% (67 to 90)	Dermatologist 1 (n = 1)	76% (53 to 92)	82% (69 to 92)
				Melanoma Fellow 2 (n = 1)	86% (64 to 97)	75% (60 to 86)	Dermatologist 2 (n = 1)	86% (64 to 97)	75% (60 to 86)
Scope 2008 Ugly duckling (i-b) 5/140; 3%	Dermatology nurse + medical photographer (n = 5)	60% (15 to 95)	96% (91 to 98)	General dermatologists (n = 13)	80% (28 to 99)	86% (79 to 91)	Expert dermatologists (n = 8)	80% (28 to 99)	95% (90 to 98)
Westerhoff 2000 No algorithm (i-b) 50/50;	GP pre-dermoscopy training (n = 37)	54% (39 to 68)	53% (38 to 67)	GP post- dermoscopy training (n = 37)	62% (47 to 75)	54% (39 to 68)	-	-	-

Table 5. Results for studies reporting data for more than one observer (*Continued*)

50%									

CI: confidence interval; **GP**: general practitioner; **in-p**: in-person; **i-b**: image-based; **obs**: observer

[a] Number of diseased/number of non-diseased (prevalence of disease), for each definition of the target condition

Table 6. Secondary analyses for alternative definitions of the target condition

Subgroup	Datasets	Participants (cases)	Diagnostic odds ratio (DOR) (95% CI)	Sensitivity (95% CI %)	Specificity (95% CI %)	Relative DOR (RDOR) (95% CI)	P value (RDOR)	P value[a] (hierarchical summary receiver-operator curves (HSROC) models)
Differences between in-person and image-based evaluations								
Detection of invasive melanoma alone								
In-person	7	6857 (208)	62.4 (17.6 to 222)	86% (68 to 94)	91% (81 to 96)	4.21 (0.62 to 28.6)	0.13	0.27
Image-based	5	599 (150)	14.8 (3.56 to 61.9)	76% (50 to 91)	83% (62 to 93)	-	-	-
Detection of any skin lesion requiring excision								
In-person	7	8091 (2187)	20.5 (7.11 to 59.3)	81% (68 to 90)	81% (56 to 93)	1.70 (0.24 to 12.3)	0.55	0.87
Image-based	3	547 (138)	11.9 (2.22 to 65.3)	75% (49 to 90)	79% (38 to 96)	-	-	-

[a] Likelihood ratio test assessing differences in both accuracy and threshold.

Table 7. Results for studies reporting data for more than one definition of the target condition

	Detection of invasive melanoma			Detection of invasive melanoma or atypical intraepidermalmelanocytic variants			Detection of any lesion requiring excision		
Study author	Dis/non-dis; prev[a]	Sensitivity (95% CIs)	Specificity (95% CIs)	Dis/non-dis; prev[a]	Sensitivity (95% CIs)	Specificity (95% CIs)	Dis/non-dis; prev[a]	Sensitivity (95% CIs)	Specificity (95% CIs)

Table 7. Results for studies reporting data for more than one definition of the target condition (*Continued*)

In-person									
Ek 2005	-	-	-	23/2559; 1%	48% (27 to 69)	99% (99 to 99)	1754 /828; 68%	98% (97 to 98)	13% (11 to 15)
McGovern 1992	6/186; 3%	100% (54 to 100)	89% (83 to 93)	11/181; 6%	73% (39 to 94)	88% (83 to 93)	15/177; 8%	73% (45 to 92)	88% (82 to 93)
Stanganelli 2000	-	-	-	55/3317; 2%	67% (53 to 79)	99% (99 to 100)	98/3274; 3%	71% (61 to 80)	99% (99 to 99)
Steiner 1987	-	-	-	73/245; 23%	59% (47 to 70)	87% (83 to 91)	93/225; 29%	67% (56 to 76)	86% (81 to 90)
Walter 2012	16/757; 2%	94% (70 to 100)	80% (77 to 83)	18/755; 2%	94% (73 to 100)	80% (77 to 83)	22/751; 3%	82% (60 to 95)	80% (77 to 83)
Image-based									
Carli 2002b	-	-	-	10/43; 19%	80% (44 to 97)	84% (69 to 93)	20/34; 37%	80% (56 to 94)	74% (56 to 87)
Rosendahl 2011	-	-	-	29/434; 6%	21% (08 to 40)	97% (95 to 98)	104/359; 22%	76% (67 to 84)	85% (81 to 88)
Stanganelli 1998a	-	-	-	10/20; 33%	40% (12 to 74)	75% (51 to 91)	14/16; 47%	64% (35 to 87)	75% (48 to 93)

[a] Number of diseased/number of non-diseased; prevalence of disease, for each definition of the target condition.

APPENDICES

Appendix 1. Current content and structure of the Programme Grant

	LIST OF REVIEWS	Number of studies
	Diagnosis of melanoma	
1	Visual inspection	49

(*Continued*)

2	Dermoscopy +/- visual inspection	104
3	Teledermatology	22
4	Smartphone applications	2
5a	Computer-assisted diagnosis - dermoscopy-based techniques	42
5b	Computer-assisted diagnosis - spectroscopy-based techniques	Review amalgamated into 5a
6	Reflectance confocal microscopy	18
7	High-frequency ultrasound	5
	Diagnosis of keratinocyte skin cancer (BCC and cSCC)	
8	Visual inspection +/- Dermoscopy	24
5c	Computer-assisted diagnosis - dermoscopy-based techniques	Review amalgamated into 5a
5d	Computer-assisted diagnosis - spectroscopy-based techniques	Review amalgamated into 5a
9	Optical coherence tomography	5
10	Reflectance confocal microscopy	10
11	Exfoliative cytology	9
	Staging of melanoma	
12	Imaging tests (ultrasound, CT, MRI, PET-CT)	38
13	Sentinel lymph node biopsy	160
	Staging of cSCC	
	Imaging tests review	Review dropped; only one study identified
13	Sentinel lymph node biopsy	Review amalgamated into 13 above (n = 15 studies)

Appendix 2. Glossary of terms

Term	Definition
Atypical intraepidermal melanocytic variant	Unusual area of darker pigmentation contained within the epidermis that may progress to an invasive melanoma; includes melanoma in situ and lentigo maligna
Atypical naevi	Unusual looking but noncancerous mole or area of darker pigmentation of the skin
BRAF V600 mutation	BRAF is a human gene that makes a protein called B-Raf which is involved in the control of cell growth. BRAF mutations (damaged DNA) occur in around 40% of melanomas, which can then be treated with particular drugs
BRAF inhibitors	Therapeutic agents that inhibit the serine-threonine protein kinase BRAF mutated metastatic melanoma
Breslow thickness	A scale for measuring the thickness of melanomas by the pathologist using a microscope, measured in mm from the top layer of skin to the bottom of the tumour
Congenital naevi	A type of mole found on infants at birth
Dermoscopy	Whereby a handheld microscope is used to allow more detailed, magnified, examination of the skin compared to examination by the naked eye alone
False-negative	An individual who is truly positive for a disease, but whom a diagnostic test classifies as disease-free
False-positive	An individual who is truly disease-free, but whom a diagnostic test classifies as having the disease
Histopathology/histology	The study of tissue, usually obtained by biopsy or excision, for example under a microscope
Incidence	The number of new cases of a disease in a given time period
Index test	A diagnostic test under evaluation in a primary study
Lentigo maligna	Unusual area of darker pigmentation contained within the epidermis that includes malignant cells but with no invasive growth. May progress to an invasive melanoma
Lymph node	Lymph nodes filter the lymphatic fluid (clear fluid containing white blood cells) that travels around the body to help fight disease; they are located throughout the body often in clusters (nodal basins)
Melanocytic naevus	An area of skin with darker pigmentation (or melanocytes) also referred to as 'moles'

(*Continued*)

Meta-analysis	A form of statistical analysis used to synthesise results from a collection of individual studies
Metastases/metastatic disease	Spread of cancer away from the primary site to somewhere else through the bloodstream or the lymphatic system
Micrometastases	Micrometastases are metastases so small that they can only be seen under a microscope
Mitotic rate	Microscopic evaluation of number of cells actively dividing in a tumour
Morbidity	Detrimental effects on health
Mortality	Either (1) the condition of being subject to death; or (2) the death rate, which reflects the number of deaths per unit of population in relation to any specific region, age group, disease, treatment or other classification, usually expressed as deaths per 100, 1000, 10,000 or 100,000 people
Multidisciplinary team	A team with members from different healthcare professions and specialties (e.g. urology, oncology, pathology, radiology, and nursing). Cancer care in the National Health Service (NHS) uses this system to ensure that all relevant health professionals are engaged to discuss the best possible care for a patient
Prevalence	The proportion of a population found to have a condition
Prognostic factors/indicators	Specific characteristics of a cancer or the person who has it, which might affect the patient's prognosis
Receiver operating characteristic (ROC) plot	A plot of the sensitivity against the inverse of the specificity of a test at different thresholds for test positivity; represents the diagnostic capability of a test with a range of binary test results
Receiver operating characteristic (ROC) analysis	The analysis of a ROC plot of a test to select an optimal threshold for test positivity
Recurrence	Recurrence is when new cancer cells are detected following treatment. This can occur either at the site of the original tumour or at other sites in the body
Reference standard	A test or combination of tests used to establish the final or 'true' diagnosis of a patient in an evaluation of a diagnostic test
Reflectance confocal microscopy (RCM)	A microscopic technique using infrared light (either in a handheld device or a static unit) that can create images of the deeper layers of the skin
Sensitivity	In this context the term is used to mean the proportion of individuals with a disease who have that disease correctly identified by the study test

(*Continued*)

Specificity	The proportion of individuals without the disease of interest (in this case with benign skin lesions) who have that absence of disease correctly identified by the study test
Staging	Clinical description of the size and spread of a patient's tumour, fitting into internationally agreed categories
Subclinical (disease)	Disease that is usually asymptomatic and not easily observable, e.g. by clinical or physical examination
Systemic treatment	Treatment, usually given by mouth or by injection, that reaches and affects cancer cells throughout the body rather than targeting one specific area

Appendix 3. Table of acronyms and abbreviations used

Acronym	Definition
3PCL	three-point checklist
7FFM	seven features for melanoma
7PCL	seven-point checklist
ABCD(E)	asymmetry, border, colour, differential structures (enlargement)
AHM	amelanotic or hypomelanotic melanoma
AK	actinic keratosis
AMN	atypical melanocytic naevi
AUC	area under the curve
BCC	basal cell carcinoma
BD	Bowen's disease
BN	benign naevi
BNM	benign non-melanocytic
BPC	between-person comparison (of tests)
CAD	computer-assisted diagnosis

(*Continued*)

CCS	case-control study
CD	compact disc
CM	cutaneous melanoma
CMM	cutaneous malignant melanoma
CS	case series
CSCC	cutaneous squamous cell carcinoma
D-	disease-negative
D+	disease-positive
DF	dermatofibroma
Dx	diagnosis
ELM	epiluminescence microscopy
FN	false-negative
FP	false-positive
FU	follow-up
GP	general practitioner
H&E	haematoxylin and eosin stain
LPLK	lichen planus-like keratosis
LS	lentigo simplex
MiS	melanoma in situ (or lentigo maligna)
MM	malignant (invasive) melanoma
MN	melanocytic naevi
MSDSLA	multispectral digital skin lesion analysis device
N/A	not applicable
NC	non comparative

(*Continued*)

NMLs	non melanocytic lesions
NPV	negative predictive value
NR	not reported
P	prospective
PCPs	primary care providers
PLC	pigmented lesion clinic
PPV	positive predictive value
PSL	pigmented skin lesion
R	retrospective
RCM	reflectance confocal microscopy
RCT	randomised controlled trial
SCC	squamous cell carcinoma
SD	standard deviation
SDDI	Short term sequential digital dermoscopy imaging
se	sensitivity
sp	specificity
SK	seborrhoeic keratosis
SN	Spitz naevi
SSM	superficial spreading melanoma
SVS	support vector system
TD	teledermatology
TN	true negative
TWR	two-week rule
VI	visual inspection

(*Continued*)

WPC	within-person comparison (of tests)
WPC-algs	within-person comparison (of algorithms)

Appendix 4. Content of algorithms used to assist melanoma diagnosis by visual inspection alone

ABCD (Friedman 1985; Rigel 1993; Pehamberger 1993) **ABCDE** (Abbasi 2004; Benelli 1999; Benelli 2001; Carli 1994; Cristofolini 1994; Thomas 1998) **BCD** (McGovern 1992)	**Seven-point checklist** (Keefe 1990; MacKie 1985; MacKie 1990)	**Seven-point checklist (revised)** (Healsmith 1994; MacKie 1990)
A - asymmetry • variable centripetal growth of melanocytes (Friedman 1985) • "geometrical asymmetry in two axes of the tumour" (Benelli 1999; Benelli 2001; Thomas 1998) • "one half does not match the other half" (McGovern 1992); not separately scored in study "because we believed that asymmetry and border irregularity were linked" B - irregular borders • irregular shape with notching or scalloping of border (Friedman 1985) • "edges are ragged, notched, or blurred" (McGovern 1992) • "irregular and notched" (Cristofolini 1994) • "unsharp or ill-defined or angular" (Thomas 1998) • "ragged or indented" (Benelli 1999; Benelli 2001) C - colour • variable pigmentation, multiple colours; various of hues of brown, also black, blue, red and white (Friedman 1985) • "pigmentation is not uniform; shades of tan, brown and black are present with dashes of red, white, or blue" (McGovern 1992) • "mottled-haphazard display"	• sensory change (greater awareness of the lesion or mild itch); • diameter of ≥ 1 cm; • growth of the lesion; • an irregular edge; • irregular pigment with different shades of brown and black in the lesion; • inflammation • crusting, oozing, or bleeding. Presence of 3 or more suggestive of melanoma	Healsmith 1994 , MacKie 1990 and Mackie 1991 describe the revised criteria as: major signs • change in size • change in shape • change in colour minor signs • inflammation • crusting or bleeding • sensory change • diameter ≥ 7 mm "a patient with a pigmented lesion with any one of the major signs should be considered for referral and that the presence of any of the minor signs should be a further stimulus to referral." (MacKie 1990)

(*Continued*)

(Cristofolini 1994) • "presence of at least two different colours within the lesion (with the exception of the usual symmetrical darkening of the lesion in its center)" (Benelli 2001; Thomas 1998) • "multiple colours" (Abbasi 2004) D - diameter equal or superior to 6 mm • all studies agree E - evolution • "changes in pigmentation" (Cristofolini 1994) • "enlargement of the surface (and not in height) of the lesion; anamnestic criterion based on the patient's description of the natural history of the lesion" (Thomas 1998) • "elevation, enlargement or change in the color of the lesion" (Benelli 1999; Benelli 2001) • "evolving (with respect to size, shape, shades of colour, surface features, or symptoms)" (Abbasi 2004) McGovern 1992 describes 7 characteristics as: "increasing size, variegation, inflammation, irregular outline, greater than 1cm diameter, itch, bleeding" These are expanded on in MacKie 1990, who describes the original (1985) criteria as: • sensory change, often described as a greater awareness of the lesion but also as a mild itch; • diameter of 1 cm or greater; • growth of the lesion; • an irregular edge; • irregular pigment with different shades of brown and black in the lesion; • inflammation (a reddish tinge within the lesion); and • crusting, oozing, or bleeding. • $\geq$ 3 criteria should prompt referral (MacKie 1990)		

Appendix 5. Proposed sources of heterogeneity

i. Population characteristics

- general versus higher risk populations
- patient population: primary/secondary/specialist unit
- lesion suspicion: general suspicion/atypical/equivocal/NR
- lesion type: any pigmented; melanocytic
- inclusion of multiple lesions per participant
- ethnicity

ii. Index test characteristics

- the nature of and definition of criteria for test positivity
- observer experience with the index test
- approaches to lesion preparation (e.g. the use of oil or antiseptic gel for dermoscopy)

iii. Reference standard characteristics

- reference standard used
- whether histology-reporting meets pathology-reporting guidelines
- use of excisional versus diagnostic biopsy
- whether two independent dermatopathologists reviewed histological diagnosis

iv. Study quality

- consecutive or random sample of participants recruited
- index test interpreted blinded to the reference standard result
- index test interpreted blinded to the result of any other index test
- presence of partial or differential verification bias (whereby only a sample of those subject to the index test are verified by the reference test or by the same reference test with selection dependent on the index test result)
- use of an adequate reference standard
- overall risk of bias

Appendix 6. Final search strategies

Database: Ovid MEDLINE(R) 1946 to August week 3 2016

Search strategy:

1 exp melanoma/
2 exp skin cancer/
3 exp basal cell carcinoma/
4 basalioma$1.ti,ab.
5 ((basal cell or skin) adj2 (cancer$1 or carcinoma$1 or mass or masses or tumour$1 or tumor$1 or neoplasm$1 or adenoma$1 or epithelioma$1 or lesion$1 or malignan$ or nodule$1)).ti,ab.
6 (pigmented adj2 (lesion$1 or mole$ or nevus or naevi or naevus or naevi or skin)).ti,ab.
7 (melanom$1 or nonmelanoma$1 or non-melanoma$1 or melanocyt$ or non-melanocyt$ or nonmelanocyt$ or keratinocyt$).ti,ab.
8 nmsc.ti,ab.
9 (squamous cell adj2 (cancer$1 or carcinoma$1 or mass or masses or tumor$1 or tumour$1 or neoplasm$1 or adenoma$1 or epithelioma$1 or epithelial or lesion$1 or malignan$ or nodule$1) adj2 (skin or epiderm$ or cutaneous)).ti,ab.
10 (BCC or CSCC or NMSC).ti,ab.
11 keratinocy$.ti,ab.
12 Keratinocytes/

13 or/1-12
14 dermoscop$.ti,ab.
15 dermatoscop$.ti,ab.
16 photomicrograph$.ti,ab.
17 exp epiluminescence microscopy/
18 (epiluminescence adj2 microscop$).ti,ab.
19 (confocal adj2 microscop$).ti,ab.
20 (incident light adj2 microscop$).ti,ab.
21 (surface adj2 microscop$).ti,ab.
22 (visual adj (inspect$ or examin$)).ti,ab.
23 ((clinical or physical) adj examin$).ti,ab.
24 3 point.ti,ab.
25 three point.ti,ab.
26 pattern analys$.ti,ab.
27 ABCD$.ti,ab.
28 menzies.ti,ab.
29 7 point.ti,ab.
30 seven point.ti,ab.
31 (digital adj2 (dermoscop$ or dermatoscop$)).ti,ab.
32 artificial intelligence.ti,ab.
33 AI.ti,ab.
34 computer assisted.ti,ab.
35 computer aided.ti,ab.
36 neural network$.ti,ab.
37 exp diagnosis, computer-assisted/
38 MoleMax.ti,ab.
39 image process$.ti,ab.
40 automatic classif$.ti,ab.
41 image analysis.ti,ab.
42 SIAscop$.ti,ab.
43 Aura.ti,ab.
44 (optical adj2 scan$).ti,ab.
45 MelaFind.ti,ab.
46 SIMSYS.ti,ab.
47 MoleMate.ti,ab.
48 SolarScan.ti,ab.
49 VivaScope.ti,ab.
50 (high adj3 ultraso$).ti,ab.
51 (canine adj2 detect$).ti,ab.
52 ((mobile or cell or cellular or smart) adj ((phone$1 adj2 app$1) or application$1)).ti,ab.
53 smartphone$.ti,ab.
54 (DermoScan or SkinVision or DermLink or SpotCheck).ti,ab.
55 Mole Detective.ti,ab.
56 Spot Check.ti,ab.
57 (mole$1 adj2 map$).ti,ab.
58 (total adj2 body).ti,ab.
59 exfoliative cytolog$.ti,ab.
60 digital analys$.ti,ab.
61 (image$1 adj3 software).ti,ab.
62 (teledermatolog$ or tele-dermatolog$ or telederm or tele-derm or teledermoscop$ or tele-dermoscop$ or teledermatoscop$ or tele-dermatoscop$).ti,ab.
63 (optical coherence adj (technolog$ or tomog$)).ti,ab.
64 (computer adj2 diagnos$).ti,ab.

65 exp sentinel lymph node biopsy/
66 (sentinel adj2 node).ti,ab.
67 naevisense.mp. or HFUS.ti,ab.
68 electrical impedance spectroscopy.ti,ab.
69 history taking.ti,ab.
70 patient history.ti,ab.
71 (naked eye adj (exam$ or assess$)).ti,ab.
72 (skin adj exam$).ti,ab.
73 physical examination/
74 ugly duckling.mp. or UD.ti,ab.
75 ((physician$ or clinical or physical) adj (exam$ or triage or recog$)).ti,ab.
76 ABCDE.mp. or VOC.ti,ab.
77 clinical accuracy.ti,ab.
78 Family Practice/ or Physicians, Family/ or clinical competence/
79 (confocal adj2 microscop$).ti,ab.
80 diagnostic algorithm$1.ti,ab.
81 checklist$.ti,ab.
82 virtual imag$1.ti,ab.
83 volatile organic compound$1.ti,ab.
84 dog$1.ti,ab.
85 gene expression analy$.ti,ab.
86 reflex transmission imag$.ti,ab.
87 thermal imaging.ti,ab.
88 elastography.ti,ab.
89 or/14-88
90 (CT or PET).ti,ab.
91 PET-CT.ti,ab.
92 (FDG or F18 or Fluorodeoxyglucose or radiopharmaceutical$).ti,ab.
93 exp Deoxyglucose/
94 deoxy-glucose.ti,ab.
95 deoxyglucose.ti,ab.
96 CATSCAN.ti,ab.
97 exp Tomography, Emission-Computed/
98 exp Tomography, X-ray computed/
99 positron emission tomograph$.ti,ab.
100 exp magnetic resonance imaging/
101 (MRI or fMRI or NMRI or scintigraph$).ti,ab.
102 exp echography/
103 Doppler echography.ti,ab.
104 sonograph$.ti,ab.
105 ultraso$.ti,ab.
106 doppler.ti,ab.
107 magnetic resonance imag$.ti,ab.
108 or/90-107
109 (stage$ or staging or metasta$ or recurrence or sensitivity or specificity or false negative$ or thickness$).ti,ab.
110 "Sensitivity and Specificity"/
111 exp cancer staging/
112 or/109-111
113 108 and 112
114 89 or 113
115 13 and 114

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 29 August, 2016

Search strategy:

1 basalioma$1.ti,ab.
2 ((basal cell or skin) adj2 (cancer$1 or carcinoma$1 or mass or masses or tumour$1 or tumor$1 or neoplasm$1 or adenoma$1 or epithelioma$1 or lesion$1 or malignan$ or nodule$1)).ti,ab.
3 (pigmented adj2 (lesion$1 or mole$ or nevus or naevi or naevus or naevi or skin)).ti,ab.
4 (melanom$1 or nonmelanoma$1 or non-melanoma$1 or melanocyt$ or non-melanocyt$ or nonmelanocyt$ or keratinocyt$).ti,ab.
5 nmsc.ti,ab.
6 (squamous cell adj2 (cancer$1 or carcinoma$1 or mass or masses or tumor$1 or tumour$1 or neoplasm$1 or adenoma$1 or epithelioma$1 or epithelial or lesion$1 or malignan$ or nodule$1) adj2 (skin or epiderm$ or cutaneous)).ti,ab.
7 (BCC or CSCC or NMSC).ti,ab.
8 keratinocy$.ti,ab.
9 or/1-8
10 dermoscop$.ti,ab.
11 dermatoscop$.ti,ab.
12 photomicrograph$.ti,ab.
13 (epiluminescence adj2 microscop$).ti,ab.
14 (confocal adj2 microscop$).ti,ab.
15 (incident light adj2 microscop$).ti,ab.
16 (surface adj2 microscop$).ti,ab.
17 (visual adj (inspect$ or examin$)).ti,ab.
18 ((clinical or physical) adj examin$).ti,ab.
19 3 point.ti,ab.
20 three point.ti,ab.
21 pattern analys$.ti,ab.
22 ABCD$.ti,ab.
23 menzies.ti,ab.
24 7 point.ti,ab.
25 seven point.ti,ab.
26 (digital adj2 (dermoscop$ or dermatoscop$)).ti,ab.
27 artificial intelligence.ti,ab.
28 AI.ti,ab.
29 computer assisted.ti,ab.
30 computer aided.ti,ab.
31 neural network$.ti,ab.
32 MoleMax.ti,ab.
33 image process$.ti,ab.
34 automatic classif$.ti,ab.
35 image analysis.ti,ab.
36 SIAscop$.ti,ab.
37 Aura.ti,ab.
38 (optical adj2 scan$).ti,ab.
39 MelaFind.ti,ab.
40 SIMSYS.ti,ab.
41 MoleMate.ti,ab.
42 SolarScan.ti,ab.
43 VivaScope.ti,ab.
44 (high adj3 ultraso$).ti,ab.
45 (canine adj2 detect$).ti,ab.
46 ((mobile or cell or cellular or smart) adj ((phone$1 adj2 app$1) or application$1)).ti,ab.
47 smartphone$.ti,ab.
48 (DermoScan or SkinVision or DermLink or SpotCheck).ti,ab.
49 Mole Detective.ti,ab.
50 Spot Check.ti,ab.
51 (mole$1 adj2 map$).ti,ab.

52 (total adj2 body).ti,ab.
53 exfoliative cytolog$.ti,ab.
54 digital analys$.ti,ab.
55 (image$1 adj3 software).ti,ab.
56 (teledermatolog$ or tele-dermatolog$ or telederm or tele-derm or teledermoscop$ or tele-dermoscop$ or teledermatoscop$ or tele-dermatoscop$).ti,ab.
57 (optical coherence adj (technolog$ or tomog$)).ti,ab.
58 (computer adj2 diagnos$).ti,ab.
59 (sentinel adj2 node).ti,ab.
60 naevisense.mp. or HFUS.ti,ab.
61 electrical impedance spectroscopy.ti,ab.
62 history taking.ti,ab.
63 patient history.ti,ab.
64 (naked eye adj (exam$ or assess$)).ti,ab.
65 (skin adj exam$).ti,ab.
66 ugly duckling.mp. or UD.ti,ab.
67 ((physician$ or clinical or physical) adj (exam$ or triage or recog$)).ti,ab.
68 ABCDE.mp. or VOC.ti,ab.
69 clinical accuracy.ti,ab.
70 (Family adj (Practice or Physicians)).ti,ab.
71 (confocal adj2 microscop$).ti,ab.
72 clinical competence.ti,ab.
73 diagnostic algorithm$1.ti,ab.
74 checklist$.ti,ab.
75 virtual imag$1.ti,ab.
76 volatile organic compound$1.ti,ab.
77 dog$1.ti,ab.
78 gene expression analy$.ti,ab.
79 reflex transmission imag$.ti,ab.
80 thermal imaging.ti,ab.
81 elastography.ti,ab.
82 or/10-81
83 (CT or PET).ti,ab.
84 PET-CT.ti,ab.
85 (FDG or F18 or Fluorodeoxyglucose or radiopharmaceutical$).ti,ab.
86 deoxy-glucose.ti,ab.
87 deoxyglucose.ti,ab.
88 CATSCAN.ti,ab.
89 positron emission tomograph$.ti,ab.
90 (MRI or fMRI or NMRI or scintigraph$).ti,ab.
91 Doppler echography.ti,ab.
92 sonograph$.ti,ab.
93 ultraso$.ti,ab.
94 doppler.ti,ab.
95 magnetic resonance imag$.ti,ab.
96 or/83-95
97 (stage$ or staging or metasta$ or recurrence or sensitivity or specificity or false negative$ or thickness$).ti,ab.
98 96 and 97
99 82 or 98
100 9 and 99

Database: Embase 1974 to 29 August 2016

Search strategy:

1 *melanoma/

2 *skin cancer/
3 *basal cell carcinoma/
4 basalioma$.ti,ab.
5 ((basal cell or skin) adj2 (cancer$1 or carcinoma$1 or mass or masses or tumour$1 or tumor$1 or neoplasm$ or adenoma$ or epithelioma$ or lesion$ or malignan$ or nodule$)).ti,ab.
6 (pigmented adj2 (lesion$1 or mole$ or nevus or naevi or naevus or naevi or skin)).ti,ab.
7 (melanom$1 or nonmelanoma$1 or non-melanoma$1 or melanocyt$ or non-melanocyt$ or nonmelanocyt$ or keratinocyt$).ti,ab.
8 nmsc.ti,ab.
9 (squamous cell adj2 (cancer$1 or carcinoma$1 or mass or tumor$1 or tumour$1 or neoplasm$1 or adenoma$1 or epithelioma$1 or epithelial or lesion$1 or malignan$ or nodule$1) adj2 (skin or epiderm$ or cutaneous)).ti,ab.
10 (BCC or cscc).mp. or NMSC.ti,ab.
11 keratinocyte.ti,ab.
12 keratinocy$.ti,ab.
13 or/1-12
14 dermoscop$.ti,ab.
15 dermatoscop$.ti,ab.
16 photomicrograph$.ti,ab.
17 *epiluminescence microscopy/
18 (epiluminescence adj2 microscop$).ti,ab.
19 (confocal adj2 microscop$).ti,ab.
20 (incident light adj2 microscop$).ti,ab.
21 (surface adj2 microscop$).ti,ab.
22 (visual adj (inspect$ or examin$)).ti,ab.
23 ((clinical or physical) adj examin$).ti,ab.
24 3 point.ti,ab.
25 three point.ti,ab.
26 pattern analys$.ti,ab.
27 ABCD$.ti,ab.
28 menzies.ti,ab.
29 7 point.ti,ab.
30 seven point.ti,ab.
31 (digital adj2 (dermoscop$ or dermatoscop$)).ti,ab.
32 artificial intelligence.ti,ab.
33 AI.ti,ab.
34 computer assisted.ti,ab.
35 computer aided.ti,ab.
36 neural network$.ti,ab.
37 MoleMax.ti,ab.
38 exp diagnosis, computer-assisted/
39 image process$.ti,ab.
40 automatic classif$.ti,ab.
41 image analysis.ti,ab.
42 SIAscop$.ti,ab.
43 (optical adj2 scan$).ti,ab.
44 Aura.ti,ab.
45 MelaFind.ti,ab.
46 SIMSYS.ti,ab.
47 MoleMate.ti,ab.
48 SolarScan.ti,ab.
49 VivaScope.ti,ab.
50 confocal microscop$.ti,ab.
51 (high adj3 ultraso$).ti,ab.
52 (canine adj2 detect$).ti,ab.

53 ((mobile or cell$ or cellular or smart) adj ((phone$1 adj2 app$1) or application$1)).ti,ab.
54 smartphone$.ti,ab.
55 (DermoScan or SkinVision or DermLink or SpotCheck).ti,ab.
56 Spot Check.ti,ab.
57 Mole Detective.ti,ab.
58 (mole$1 adj2 map$).ti,ab.
59 (total adj2 body).ti,ab.
60 exfoliative cytolog$.ti,ab.
61 digital analys$.ti,ab.
62 (image$1 adj3 software).ti,ab.
63 (optical coherence adj (technolog$ or tomog$)).ti,ab.
64 (teledermatolog$ or tele-dermatolog$ or telederm or tele-derm or teledermoscop$ or tele-dermoscop$ or teledermatoscop$).mp. or tele-dermatoscop$.ti,ab.
65 (computer adj2 diagnos$).ti,ab.
66 *sentinel lymph node biopsy/
67 (sentinel adj2 node).ti,ab.
68 naevisense.ti,ab.
69 HFUS.ti,ab.
70 electrical impedance spectroscopy.ti,ab.
71 history taking.ti,ab.
72 patient history.ti,ab.
73 (naked eye adj (exam$ or assess$)).ti,ab.
74 (skin adj exam$).ti,ab.
75 *physical examination/
76 ugly duckling.ti,ab.
77 UD sign$.ti,ab.
78 ((physician$ or clinical or physical) adj (exam$ or recog$ or triage)).ti,ab.
79 ABCDE.ti,ab.
80 clinical accuracy.ti,ab.
81 *general practice/
82 (confocal adj2 microscop$).ti,ab.
83 clinical competence/
84 diagnostic algorithm$.ti,ab.
85 checklist$1.ti,ab.
86 virtual image$1.ti,ab.
87 volatile organic compound$1.ti,ab.
88 VOC.ti,ab.
89 dog$1.ti,ab.
90 gene expression analys$.ti,ab.
91 reflex transmission imaging.ti,ab.
92 thermal imaging.ti,ab.
93 elastography.ti,ab.
94 dog$1.ti,ab.
95 gene expression analys$.ti,ab.
96 reflex transmission imaging.ti,ab.
97 thermal imaging.ti,ab.
98 elastography.ti,ab.
99 or/14-93
100 PET-CT.ti,ab.
101 (CT or PET).ti,ab.
102 (FDG or F18 or Fluorodeoxyglucose or radiopharmaceutical$).ti,ab.
103 exp Deoxyglucose/
104 CATSCAN.ti,ab.

105 deoxyglucose.ti,ab.
106 deoxy-glucose.ti,ab.
107 *positron emission tomography/
108 *computer assisted tomography/
109 positron emission tomograph$.ti,ab.
110 *nuclear magnetic resonance imaging/
111 (MRI or fMRI or NMRI or scintigraph$).ti,ab.
112 *echography/
113 Doppler.ti,ab.
114 sonograph$.ti,ab.
115 ultraso$.ti,ab.
116 magnetic resonance imag$.ti,ab.
117 or/100-116
118 (stage$ or staging or metasta$ or recurrence or sensitivity or specificity or false negative$ or thickness$).ti,ab.
119 "Sensitivity and Specificity"/
120 *cancer staging/
121 or/118-120
122 117 and 121
123 99 or 122
124 13 and 123

Database: Cochrane Library (Wiley) 2016 searched 30 August 2016 CDSR Issue 8 of 12 2016 CENTRAL Issue 7 of 12 2016 HTA Issue 3 of 4 July 2016 DARE Issue 3 of 4 2015

Search strategy:
#1 melanoma* or nonmelanoma* or non-melanoma* or melanocyt* or non-melanocyt* or nonmelanocyt* or keratinocyte*
#2 MeSH descriptor: [Melanoma] explode all trees
#3 "skin cancer*"
#4 MeSH descriptor: [Skin Neoplasms] explode all trees
#5 skin near/2 (cancer* or carcinoma* or mass or masses or tumour* or tumor* or neoplasm* or adenoma* or epithelioma* or lesion* or malignan* or nodule*)
#6 nmsc
#7 "squamous cell" near/2 (cancer* or carcinoma* or mass or masses or tumour* or tumor* or neoplasm* or adenoma* or epithelioma* or lesion* or malignan* or nodule*) near/2 (skin or epiderm* or cutaneous)
#8 "basal cell" near/2 (cancer* or carcinoma* or mass or masses or tumour* or tumor* or neoplasm* or adenoma* or epithelioma* or lesion* or malignan* or nodule*)
#9 pigmented near/2 (lesion* or nevus or mole* or naevi or naevus or naevi or skin)
#10 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9
#11 dermoscop*
#12 dermatoscop*
#13 Photomicrograph*
#14 MeSH descriptor: [Dermoscopy] explode all trees
#15 confocal near/2 microscop*
#16 epiluminescence near/2 microscop*
#17 incident next light near/2 microscop*
#18 surface near/2 microscop*
#19 "visual inspect*"
#20 "visual exam*"
#21 (clinical or physical) next (exam*)
#22 "3 point"
#23 "three point"
#24 "pattern analys*"
#25 ABDC
#26 menzies
#27 "7 point"

#28 “seven point”
#29 digital near/2 (dermoscop* or dermatoscop*)
#30 “artificial intelligence”
#31 “AI”
#32 “computer assisted”
#33 “computer aided”
#34 AI
#35 “neural network*”
#36 MoleMax
#37 “computer diagnosis”
#38 “image process*”
#39 “automatic classif*”
#40 SIAscope
#41 “image analysis”
#42 “optical near/2 scan*”
#43 Aura
#44 MelaFind
#45 SIMSYS
#46 MoleMate
#47 SolarScan
#48 Vivascope
#49 “confocal microscopy”
#50 high near/3 ultraso*
#51 canine near/2 detect*
#52 Mole* near/2 map*
#53 total near/2 body
#54 mobile* or smart near/2 phone*
#55 cell next phone*
#56 smartphone*
#57 “mitotic index”
#58 DermoScan or SkinVision or DermLink or SpotCheck
#59 “Mole Detective”
#60 “Spot Check”
#61 mole* near/2 map*
#62 total near/2 body
#63 “exfoliative cytolog*”
#64 “digital analys*”
#65 image near/3 software
#66 teledermatolog* or tele-dermatolog* or telederm or tele-derm or teledermoscop* or tele-dermoscop* or teledermatoscop* or tele-dermatolog*
#67 “optical coherence” next (technolog* or tomog*)
#68 computer near/2 diagnos*
#69 sentinel near/2 node*
#70 #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69
#71 ultraso*
#72 sonograph*
#73 MeSH descriptor: [Ultrasonography] explode all trees
#74 Doppler
#75 CT or PET or PET-CT
#76 “CAT SCAN” or “CATSCAN”

#77 MeSH descriptor: [Positron-Emission Tomography] explode all trees
#78 MeSH descriptor: [Tomography, X-Ray Computed] explode all trees
#79 MRI
#80 MeSH descriptor: [Magnetic Resonance Imaging] explode all trees
#81 MRI or fMRI or NMRI or scintigraph*
#82 "magnetic resonance imag*"
#83 MeSH descriptor: [Deoxyglucose] explode all trees
#84 deoxyglucose or deoxy-glucose
#85 "positron emission tomograph*"
#86 #71 or #72 or #73 or #74 or #75 or #76 or #77 or #78 or #79 or #80 or #81 or #82 or #83 or #84 or #85
#87 stage* or staging or metasta* or recurrence or sensitivity or specificity or "false negative*" or thickness*
#88 MeSH descriptor: [Neoplasm Staging] explode all trees
#89 #87 or #88
#90 #89 and #86
#91 #70 or #90
#92 #10 and #91
#93 BCC or CSCC or NMCS
#94 keratinocy*
#95 #93 or #94
#96 #10 or #95
#97 naevisense
#98 HFUS
#99 "electrical impedance spectroscopy"
#100 "history taking"
#101 "patient history"
#102 naked next eye near/1 (exam* or assess*)
#103 skin next exam*
#104 "ugly duckling" or (UD sign*)
#105 MeSH descriptor: [Physical Examination] explode all trees
#106 (physician* or clinical or physical) near/1 (exam* or recog* or triage*)
#107 ABCDE
#108 "clinical accuracy"
#109 MeSH descriptor: [General Practice] explode all trees
#110 confocal near microscop*
#111 "diagnostic algorithm*"
#112 MeSH descriptor: [Clinical Competence] explode all trees
#113 checklist*
#114 "virtual image*"
#115 "volatile organic compound*"
#116 dog or dogs
#117 VOC
#118 "gene expression analys*"
#119 "reflex transmission imaging"
#120 "thermal imaging"
#121 elastography
#122 #97 or #98 or #99 or #100 or #101 or #102 or #103 or #104 or #105 or #106 or #107 or #108 or #109 or #110 or #111 or #112 or #113 or #114 or #115 or #116 or #117 or #118 or #119 or #120 or #121
#123 #70 or #122
#124 #96 and #123
#125 #96 and #90
#126 #125 or #124
#127 #10 and #126

Database : CINAHL Plus (EBSCO) 1937 to 30 August 2016

Search strategy:
S1 (MH "Melanoma") OR (MH "naevi and Melanomas+")
S2 (MH "Skin Neoplasms+")
S3 (MH "Carcinoma, Basal Cell+")
S4 basalioma*
S5 (basal cell) N2 (cancer* or carcinoma* or mass or masses or tumor* or tumour* or neoplasm* or adenoma* or epithelioma* or lesion* or malignan* or nodule*)
S6 (pigmented) N2 (lesion* or mole* or nevus or naevi or naevus or naevi or skin)
S7 melanom* or nonmelanoma* or non-melanoma* or melanocyt* or non-melanocyt* or nonmelanocyt*
S8 nmsc
S9 TX BCC or cscc or NMSC
S10 (MH "Keratinocytes")
S11 keratinocyt*
S12 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11
S13 dermoscop* or dermatoscop* or photomicrograph* or (3 point) or (three point) or ABCD* or menzies or (7 point) or (seven point) or AI or Molemax or SIASCOP* or Aura or MelaFind or SIMSYS or MoleMate or SolarScan or smartphone* or DermoScan or SkinVision or DermLink or SpotCheck
S14 (epiluminescence or confocal or incident or surface) N2 (microscop*)
S15 visual N1 (inspect* or examin*)
S16 (clinical or physical) N1 (examin*)
S17 pattern analys*
S18 (digital) N2 (dermoscop* or dermatoscop*)
S19 (artificial intelligence)
S20 (computer) N2 (assisted or aided)
S21 (neural network*)
S22 (MH "Diagnosis, Computer Assisted+")
S23 (image process*)
S24 (automatic classif*)
S25 (image analysis)
S26 SIAScop*
S27 (optical) N2 (scan*)
S28 (high) N3 (ultraso*)
S29 elastography
S30 (mobile or cell or cellular or smart) N2 (phone*) N2 (app or application*)
S31 (mole*) N2 (map*)
S32 total N2 body
S33 exfoliative cytolog*
S34 digital analys*
S35 image N3 software
S36 teledermatolog* or tele-dermatolog* or telederm or tele-derm or teledermoscop* or tele-dermoscop* or teledermatoscop* or tele-dermatoscop* teledermatolog* or tele-dermatolog* or telederm or tele-derm or teledermoscop*
S37 (optical coherence) N1 (technolog* or tomog*)
S38 computer N2 diagnos*
S39 sentinel N2 node
S40 (MH "Sentinel Lymph Node Biopsy")
S41 naevisense or HFUS or checklist* or VOC or dog*
S42 electrical impedance spectroscopy
S43 history taking
S44 "Patient history"
S45 naked eye
S46 skin exam*
S47 physical exam*
S48 ugly duckling

S49 UD sign*
S50 (physician* or clinical or physical) N1 (exam*)
S51 clinical accuracy
S52 general practice
S53 (physician* or clinical or physical) N1 (recog* or triage)
S54 confocal microscop*
S55 clinical competence
S56 diagnostic algorithm*
S57 checklist*
S58 virtual image*
S59 volatile organic compound*
S60 gene expression analys*
S61 reflex transmission imag*
S62 thermal imaging
S63 S13 or S14 or S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62
S64 CT or PET
S65 PET-CT
S66 FDG or F18 or Fluorodeoxyglucose or radiopharmaceutical*
S67 (MH "Deoxyglucose+")
S68 deoxy-glucose or deoxyglucose
S69 CATSCAN
S70 CAT-SCAN
S71 (MH "Deoxyglucose+")
S72 (MH "Tomography, Emission-Computed+")
S73 (MH "Tomography, X-Ray Computed")
S74 positron emission tomograph*
S75 (MH "Magnetic Resonance Imaging+")
S76 MRI or fMRI or NMRI or scintigraph*
S77 echography
S78 doppler
S79 sonograph*
S80 ultraso*
S81 magnetic resonance imag*
S82 S64 OR S65 OR S66 OR S67 OR S68 OR S69 OR S70 OR S71 OR S72 OR S73 OR S74 OR S75 OR S76 OR S77 OR S78 OR S79 OR S80 OR S81
S83 stage* or staging or metasta* or recurrence or sensitivity or specificity or (false negative*) or thickness
S84 (MH "Neoplasm Staging")
S85 S83 OR S84
S86 S82 AND S85
S87 S63 OR S86
S88 S12 AND S87

Database: Science Citation Index SCI Expanded (Web of Science) 1900 to 30 August 2016
Conference Proceedings Citation Index (Web of Science) 1900 to 1 September 2016

Search strategy:
#1 (melanom* or nonmelanom* or non-melanoma* or melanocyt* or non-melanocyt* or nonmelanocyt* or keratinocyt*)
#2 (basalioma*)
#3 ((skin) near/2 (cancer* or carcinoma or mass or masses or tumour* or tumor* or neoplasm* or adenoma* or epithelioma* or lesion* or malignan* or nodule*))
#4 ((basal) near/2 (cancer* or carcinoma* or mass or masses or tumour* or tumor* or neoplasm* or adenoma* or epithelioma* or lesion* or malignan* or nodule*))

#5 ((pigmented) near/2 (lesion* or mole* or nevus or naevi or naevus or naevi or skin))
#6 (nmsc or BCC or NMSC or keratinocy*)
#7 ((squamous cell (cancer* or carcinoma* or mass or masses or tumour* or tumor* or neoplasm* or adenoma* or epithelioma* or lesion* or malignan* or nodule*))
#8 (skin or epiderm* or cutaneous)
#9 #8 AND #7
#10 #9 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
#11 ((dermoscop* or dermatoscop* or photomicrograph* or epiluminescence or confocal or "incident light" or "surface microscop*" or "visual inspect*" or "physical exam*" or 3 point or three point or pattern analy* or ABCDE or menzies or 7 point or seven point or dermoscop* or dermatoscop* or AI or artificial or computer aided or computer assisted or neural network* or Molemax or image process* or automatic classif* or image analysis or siascope or optical scan* or Aura or melafind or simsys or molemate or solarscan or vivascope or confocal microscop* or high ultraso* or canine detect* or cellphone* or mobile* or phone* or smartphone or dermoscan or skinvision or dermlink or spotcheck or spot check or mole detective or mole map* or total body or exfoliative psychology or digital or image software or optical coherence or teledermatology or telederm* or teledermoscop* or teledermatoscop* or computer diagnos* or sentinel))
#12 ((naevisense or HFUS or impedance spectroscopy or history taking or patient history or naked eye or skin exam* or physical exam* or ugly duckling or UD sign* or physician* exam* or physical exam* or ABCDE or clinical accuracy or general practice or confocal microscop* or clinical competence or diagnostic algorithm* or checklist* or virtual image* or volatile organic or VOC or dog* or gene expression or reflex transmission or thermal imag* or elastography))
#13 #11 or #12
#14 ((PET or CT or FDG or deoxyglucose or deoxy-glucose or fluorodeoxy* or radiopharma* or CATSCAN or positron emission or computer assisted or nuclear magnetic or MRI or FMRI or NMRI or scintigraph* or echograph* or Doppler or sonograph* or ultraso* or magnetic reson*))
#15 ((stage* or staging or metast* or recurrence or sensitivity or specificity or false negative* or thickness*))
#16 #14 AND #15
#17 #16 OR #13
#18 #10 AND #17
Refined by: DOCUMENT TYPES: (MEETING ABSTRACT OR PROCEEDINGS PAPER)

Appendix 7. Full text inclusion criteria

Criterion	Inclusion	Exclusion
Study design	**For diagnostic and staging reviews** • Any study for which a 2×2 contingency table can be extracted, e.g. ○ diagnostic case control studies ○ 'cross-sectional' test accuracy study with retrospective or prospective data collection ○ studies where estimation of test accuracy was not the primary objective but test results for both index and reference standard were available ○ RCTs of tests or testing strategies where participants were randomised between index tests and all undergo a reference standard (i.e. accuracy RCTs)	• < 5 melanoma cases (diagnosis reviews) • < 10 participants (staging reviews) • Studies developing new criteria for diagnosis unless a separate 'test set' of images were used to evaluate the criteria (mainly digital dermoscopy) • Studies using 'normal' skin as controls • Letters, editorials, comment papers, narrative reviews • Insufficient data to construct a 2×2 table

(*Continued*)

Target condition	• Melanoma
	• Keratinocyte skin cancer (or non-melanoma skin cancer)
	  ○ BCC or epithelioma
	  ○ cSCC
		• Studies exclusively conducted in children
		• Studies of non-cutaneous melanoma or SCC

Population	**For diagnostic reviews** • Adults with a skin lesion suspicious for melanoma, BCC, or cSCC (other terms include pigmented skin lesion/naevi, melanocytic, keratinocyte, etc.) • Adults at high risk of developing melanoma skin cancer, BCC, or cSCC **For staging reviews** • Adults with a diagnosis of melanoma or cSCC undergoing tests for staging of lymph nodes or distant metastases or both	• People suspected of other forms of skin cancer • Studies conducted exclusively in children
Index tests	**For diagnosis** • Visual inspection/clinical examination • Dermoscopy/dermatoscopy • Teledermoscpoy • Smartphone/mobile phone applications • Digital dermoscopy/artificial intelligence • Confocal microscopy • Ocular coherence tomography • Exfoliative cytology • High-frequency ultrasound • Canine odour detection • DNA expression analysis/gene chip analysis • Other **For staging** • CT • PET • PET-CT • MRI • Ultrasound +/fine needle aspiration cytology FNAC • SLNB +/high-frequency ultrasound • Other Any test combination and in any order Any test positivity threshold Any variation in testing procedure (e.g. radioisotope used)	• Sentinel lymph biopsy for therapeutic rather than staging purposes • Tests to determine melanoma thickness • Tests to determine surgical margins/lesion borders • Tests to improve histopathology diagnose • LND
Reference standard	**For diagnostic studies** • Histopathology of the excised lesion • Clinical follow-up of non-excised/benign appearing lesions with later histopathology if	**For diagnostic studies** • Exclude if any disease-positive participants have diagnosis unconfirmed by histology • Exclude if > 50% of disease-negative

(*Continued*)

	suspicious • Expert diagnosis (studies should not be included if expert diagnosis is the sole reference standard) **For studies of imaging tests for staging** • Histopathology (via LND or SLMB) • Clinical/radiological follow-up • A combination of the above **For studies of SLNB accuracy for staging** • LND of both SLN+ and SLn participants to identify all diseased nodes • LND of SLN+ participants and follow-up of SLN participants to identify a subsequent nodal recurrence in a *previously investigated* nodal basin	participants have diagnosis confirmed by expert opinion with no histology or follow-up • Exclude studies of referral accuracy, i.e. comparing referral decision with expert diagnosis, unless evaluations of teledermatology or mobile phone applications

BCC: basal cell carcinoma; **cSCC**: cutaneous squamous cell carcinoma; **CT**: computed tomography; **FNAC**: fine needle aspiration cytology; **LND**: lymph node dissection; **MRI**: magnetic resonance imaging; **PET**: positron emission tomography; **PET-CT**: positron emission tomography computed tomography; **RCT**: randomised controlled trial; **SCC**: squamous cell carcinoma; **SLN+**: positive sentinel lymph node; **SLn**: negative sentinel lymph node; **SLNB**: sentinel lymph node biopsy

Appendix 8. Quality assessment (based on QUADAS-2)

We tailored the QUADAS-2 checklist (Whiting 2011) to the review topic as follows below.

Patient selection domain (1)

Selective recruitment of study participants can be a key influence on test accuracy. In general terms, all participants eligible to undergo a test should be included in a study, allowing for the intended use of that test within the context of the study. We considered studies that separately sampled malignant and benign lesions to have used a case-control design; and those that supplemented a series of suspicious lesions with additional malignant or benign lesions to be at unclear risk of bias

In terms of exclusions, we considered studies that excluded particular lesion types (e.g. lentigo maligna), particular lesion sites, or that excluded lesions on the basis of image quality or lack of observer agreement (e.g. on histopathology) to be at high risk of bias.

In judging the applicability of patient populations to the review question, we considered restriction to particular lesion populations, such as melanocytic, nodular, high risk or restrictions by size to be of high concern for applicability.

Given that diagnosis of skin cancer is primarily lesion-based, there is the potential for study participants with multiple lesions to contribute disproportionately to estimates of test accuracy, especially if they are at particular risk of having skin cancer. We considered studies that included a high number of lesions in relation to the number of study to be less representative than studies conducted in a more general population participants (i.e. if the difference between the number of included lesions and number of included participants is greater than 5%).

Index test domain (2)

Given the potential for subjective differences in test interpretation for melanoma, the interpretation of the index test blinded to the result of the reference standard is a key means of reducing bias. For prospective studies and retrospective studies that used the original index test interpretation, the diagnosis will by nature be interpreted and recorded before the result of the reference standard is known; however, studies using previously acquired images could be particularly susceptible to information bias. For these studies to be at low risk of bias, we required a clear indication that observers were unaware of the reference standard diagnosis at time of test interpretation. We also added an item to assess the presence of blinding between interpretations of different algorithms, however we did not include this item in the overall assessment of risk of bias.

We considered pre-specification of the index test threshold to be present if the study clearly reported that the threshold used was not data driven, that is, was not based on study results. Studies that did not clearly describe the threshold used but that required clinicians to record a diagnosis or management decision for a lesion, we considered to be unclear on this criterion. Studies reporting accuracy for multiple numeric thresholds, where ROC analysis was used to select the threshold, or that reported accuracy for the presence of independently significant lesion characteristics with no separate test set of lesions, we considered at high risk of bias.

In terms of applicability of the index test to the review question, we required the test to be applied and interpreted as it would be in a clinical practice setting, that is, in-person or face-to-face with the patient, and by a single observer as opposed to a consensus decision or average across multiple observers. We considered image-based studies to be high concern, although reflectance confocal microscopy (RCM) image interpretations where the observer was also supplied with a clinical or dermoscopic image of the lesion along with some patient characteristics were considered 'unclear'.

Despite the often subjective nature of test interpretation, it is also important for study authors to outline the particular lesion characteristics that were considered to be indicative for melanoma, particularly where established algorithms or checklists were not used. We considered studies to be of low concern if the threshold used was established in a prior study or sufficient threshold details were presented to allow replication.

The experience of the examiner will also impact on the applicability of study results. We required studies to describe the test interpreter as 'experienced' or 'expert' in RCM to have low concern about applicability.

Reference standard domain (3)

In an ideal study, consecutively recruited participants should all undergo incisional or excisional biopsy of the skin lesion regardless of level of clinical suspicion of melanoma. In reality, both partial and differential verification bias are likely. Partial verification bias may occur where histology is the only reference standard used, and only those participants with a certain degree of suspicion of malignancy based on the result of the index test undergo verification, the others either being excluded from the study or defined as being disease-negative without further assessment or follow-up, as discussed above.

Differential verification bias will be present where other reference standards are used in addition to histological verification of suspicious lesions. A typical example of verification bias in skin cancer occurs when investigators do not biopsy people with benign-appearing lesions but instead follow them up for a period of time to determine whether any malignancy subsequently develops (these would be false-negatives on the index test). We defined an 'adequate' reference standard as: all disease-positive individuals having a histological reference standard either at the time of application of the index test or after a period of clinical follow-up; and at least 80% of disease-negative participants have received a histological diagnosis, with up to 20% undergoing at least three months' follow-up of benign-appearing lesions.

A further challenge is the potential for incorporation bias, that is, where the result of the index test is used to help determine the reference standard diagnosis. It is normal practice for the clinical diagnosis (usually by visual inspection or dermoscopy) to be included on pathology request forms and for the histopathologist to use this diagnosis to help with the pathology interpretation. Although inclusion of such clinical information on the histopathology request form is theoretically a form of incorporation bias, blinded interpretation of the histopathology reference standard is not normal practice, and enforcement of such conditions would significantly limit the generalisability of the study results. For studies evaluating RCM, we divided this item into two questions, firstly whether the reference standard was blinded to the index test result (RCM), and secondly whether it was blinded to the clinical diagnosis. We included only the response to the first part (i.e. blinding to RCM) in our overall assessment of risk of bias for the reference standard domain.

In judging the applicability of the reference standard to our review question, we scored studies as high concern around applicability if they used expert diagnosis (with no follow-up) as a reference standard in any participant, or did not report histology interpretation by a dermatopathologist.

Flow and timing domain (4)

In the ideal study, the diagnosis based on the index test and reference standard should be made consecutively or as near to each other in time as possible to avoid changes in lesion over time. For lesions with a histological reference standard, we have defined a one-month period as an appropriate interval between application of the index test and the reference standard. For studies using clinical follow-up, we defined a minimum three-month follow-up period as at low risk of bias for detecting false-negatives. We chose this interval based on a study showing that most false-negative melanomas will be diagnosed within three months of the initial negative index test although a small number will be diagnosed up to 12 months subsequently (Altamura 2008).

In assessing whether all participants were included in the analysis, we considered studies at high risk of bias if they excluded participants following recruitment.

Comparative domain

We added a comparative domain to the QUADAS-2 checklist for studies comparing the accuracy of RCM and dermoscopy. We included items to assess the presence of blinding of interpretation between tests, and to specify a maximum one-month interval between application of index tests, as intervals greater than these may be accompanied by changes in tumour characteristics. As it would not be normal practice for RCM to be interpreted blinded to the clinical or dermoscopic diagnosis, the scoring of this item did not contribute to our overall assessment of risk of bias. We also considered whether both tests were applied and interpreted in a clinically applicable manner.

The following tables use text that was originally published in the QUADAS-2 tool by Whiting and colleagues *(*Whiting 2011*)*.

Item	Response (delete as required)
Participant selection 1. Risk of bias	
1. Was a consecutive or random sample of participants or images enrolled?	**Yes** - if paper states consecutive or random **No** - if paper describes other method of sampling **Unclear** - if participant sampling not described
2. Was a case-control design avoided?	**Yes** - if consecutive or random or case-control design clearly not used **No** - if study described as case-control or describes sampling specific numbers of participants with particular diagnoses **Unclear** - if not described
3. Did the study avoid inappropriate exclusions, e.g. • 'difficult-to-diagnose' lesions not excluded • lesions not excluded on basis of disagreement between evaluators	**Yes** if inappropriate exclusions were avoided **No** - if lesions were excluded that might affect test accuracy, e.g. 'difficult-to-diagnose' lesions, or where disagreement between evaluators was observed **Unclear** - if not clearly reported but there is suspicion that difficult-to-diagnose lesions may have been excluded
4. For between-person comparative studies only (i.e. allocating different tests to different study participants): • **A.** were the same participant selection criteria used for those allocated to each test? • **B.** was the potential for biased allocation between tests avoided through adequate generation of a randomised sequence? • **C.** was the potential for biased allocation between tests avoided through concealment of allocation prior to assignment?	**For A** • **Yes** - if same selection criteria were used for each index test, • **No** - if different selection criteria were used for each index test, • **Unclear** - if selection criteria per test were not described, • **N/A** - if only 1 index test was evaluated or all participants received all tests **For B** • **Yes** - if adequate randomisation procedures are described, • **No** - if inadequate randomisation procedures are described, • **Unclear** - if the method of allocation to groups is not described (a description of 'random' or 'randomised' is insufficient), • **N/A** - if only 1 index test was evaluated or all participants received all tests **For C** • **Yes** - if appropriate methods of allocation concealment are described, • **No** - if appropriate methods of allocation concealment are not described,

(*Continued*)

	• **Unclear** - if the method of allocation concealment is not described (sufficient detail to allow a definite judgement is required), • **N/A** - if only 1 index test was evaluated
Could the selection of participants have introduced bias? **For non-comparative and within-person-comparative studies** 1. If answers to all of questions 1, 2, and 3 'Yes' 2. If answers to any 1 of questions 1, 2, or 3 'No' 3. If answers to any 1 of questions 1, 2, or 3 'Unclear' **For between-person comparative studies** 1. If answers to all of questions 1, 2, 3, and 4 'Yes' 2. If answers to any 1 of questions 1, 2, 3, or 4 'No' 3. If answers to any 1 of questions 1, 2, 3, or 4 'Unclear'	**For non-comparative and within-person-comparative studies** 1. Risk is low 2. Risk is high 3. Risk unclear **For between-person comparative studies** 1. Risk is low 2. Risk is high 3. Risk unclear
Participant selection 1. Concerns regarding applicability	
1. Are the included participants and chosen study setting appropriate to answer the review question, i.e. are the study results generalisable? • This item is not asking whether exclusion of certain participant groups might bias the study's results (as in Risk of bias above), but is asking whether the chosen study participants and setting are appropriate to answer our review question. Because we are looking to establish test accuracy in both primary presentation and referred participants, a study could be appropriate for 1 setting and not for the other, or it could be unclear as to whether the study can appropriately answer either question • For each study assessed, please consider whether it is more relevant for A, participants with a primary presentation of a skin lesion or B, referred participants, and respond to the questions in either A or B accordingly. If the study gives insufficient details, please respond **Unclear** to both parts of the question	**A. For studies that will contribute to the analysis of participants with a primary presentation of a skin lesion (i.e. test naive)** • **Yes** - if participants included in the study appear to be generally representative of those who might present in a usual practice setting • **No** - if study participants appear to be unrepresentative of usual practice, e.g. in terms of severity of disease, demographic features, presence of differential diagnosis or comorbidity, setting of the study, and previous testing protocols • **Unclear** - if insufficient details are provided to determine the generalisability of study participants **B. For studies that will contribute to the analysis of referred participants (i.e. who have already undergone some form of testing)** • **Yes** - if study participants appear to be representative of those who might be referred for further investigation. If the study focuses only on those with equivocal lesions, for example, we would suggest that this is not representative of the wider referred population • **No** - if study participants appear to be unrepresentative of usual practice, e.g. if a particularly high proportion of participants have been self-referred or referred for cosmetic reasons. Other factors to consider include severity of disease, demographic features, presence of differential diagnosis or comorbidity, setting of the study, and previous testing protocols • **Unclear** - if insufficient details are provided to determine the generalisability of study participants
2. Did the study **avoid including** participants with multiple lesions?	• **Yes** - if the difference between the number of included lesions and number of included participants is less than 5% • **No** - if the difference between the number of included

(*Continued*)

	lesions and number of included participants is greater than 5% • **Unclear -** if it is not possible to assess
Is there concern that the included participants do not match the review question? 1. If the answer to question 1 or 2 'Yes' 2. If the answer to question 1 or 2 'No' 3. If the answer to question 1 or 2 'Unclear'	1. Concern is low 2. Concern is high 3. Concern is unclear
Index test 2. Risk of bias (to be completed per test evaluated)	
1. Was the index test or testing strategy result interpreted without knowledge of the results of the reference standard?	• **Yes** - if index test described as interpreted without knowledge of reference standard result or, for prospective studies, if index test is always conducted and interpreted prior to the reference standard • **No** - if index test described as interpreted in knowledge of reference standard result • **Unclear** - if index test blinding is not described
2. Was the diagnostic threshold at which the test was considered positive (i.e. melanoma present) prespecified?	• **Yes** - if threshold was prespecified (i.e. prior to analysing study results) • **No** - if threshold was not prespecified • **Unclear** - if not possible to tell whether or not diagnostic threshold was prespecified
3. For within-person comparisons of index tests or testing strategies (i.e. > 1 index test applied per participant), was each index test result interpreted without knowledge of the results of other index tests or testing strategies?	• **Yes** - if all index tests were described as interpreted without knowledge of the results of the others • **No** - if the index tests were described as interpreted in the knowledge of the results of the others • **Unclear** - if it is not possible to tell whether knowledge of other index tests could have influenced test interpretation • **N/A** - if only 1 index test was evaluated
Could the conduct or interpretation of the index test have introduced bias? **For non-comparative and between-person comparison studies** 1. If answers to questions 1 and 2 'Yes' 2. If answers to either questions 1 or 2 'No' 3. If answers to either questions 1 or 2 'Unclear' **For within-person comparative studies** 1. If answers to all questions 1, 2, for any index test and 3 'Yes' 2. If answers to any 1 of questions 1 or 2 for any index test or 3 'No' 3. If answers to any 1 of questions 1 or 2 for any index test or 3 'Unclear'	**For non-comparative and between-person comparison studies** 1. Risk is low 2. Risk is high 3. Risk is unclear **For within-person comparative studies** 1. Risk is low 2. Risk is high 3. Risk is unclear
Index test 2. Concern about applicability	

(*Continued*)

1. Was the diagnostic threshold to determine presence or absence of disease established in a previously published study? E.g. previously evaluated/established • algorithm/checklist used • lesion characteristics indicative of melanoma used • objective (usually numerical) threshold used	• **Yes** - if a previously evaluated/established tool to aid diagnosis of melanoma was used or if the diagnostic threshold used was established in a previously published study • **No** - if an unfamiliar/new tool to aid diagnosis of melanoma was used, if no particular algorithm was used, or if the objective threshold reported was chosen based on results in the current study • **Unclear** - if insufficient information was reported
2. Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication? Study results can only be reproduced if the diagnostic threshold is described in sufficient detail. This item applies equally to studies using pattern recognition and those using checklists or algorithms to aid test interpretation	• **Yes** - If the criteria for diagnosis of melanoma were reported in sufficient detail to allow replication • **No** - if the criteria for diagnosis of melanoma were not reported in sufficient detail to allow replication • **Unclear** - If some but not sufficient information on criteria for diagnosis to allow replication were provided
3. Was the test interpretation carried out by an experienced examiner?	• **Yes** - if the test was interpreted by 1 or more speciality-accredited dermatologists, or by examiners of any clinical background with special interest in dermatology and with any formal training in the use of the test • **No** - if the test was not interpreted by an experienced examiner (see above) • **Unclear** - if the experience of the examiner(s) was not reported in sufficient detail to judge or if examiners were described as 'Expert' with no further detail given • **N/A** - if system-based diagnosis, i.e. no observer interpretation
Is there concern that the index test, its conduct, or interpretation differ from the review question? 1. If answers to questions 1, 2, and 3 'Yes' 2. If answers to questions 1, 2, or 3 'No' 3. If answers to questions 1, 2, or 3 'Unclear'	1. Concern is low 2. Concern is high 3. Concern is unclear
Reference standard 3. Risk of bias	
1. Is the reference standard likely to correctly classify the target condition? **A. Disease-positive** - 1 or more of the following: • histological confirmation of melanoma following biopsy or lesion excision • clinical follow-up of benign-appearing lesions for at least 3 months following the application of the index test, leading to a histological diagnosis of melanoma **B) Disease-negative** - 1 or more of the following: • histological confirmation of absence of melanoma following biopsy or lesion excision in at least 80% of disease-negative participants • clinical follow-up of benign-appearing lesions for a	**A. Disease-positive** • **Yes** - if all participants with a final diagnosis of melanoma underwent 1 of the listed reference standards • **No** - If a final diagnosis of melanoma for any participant was reached without histopathology • **Unclear** - if the method of final diagnosis was not reported for any participant with a final diagnosis of melanoma or if the length of clinical follow-up used was not clear or if a clinical follow-up reference standard was reported in combination with a participant-based analysis and it was not possible to determine whether the detection of a malignant lesion during follow-up is the same lesion that originally tested negative on the index test

(*Continued*)

minimum of 3 months following the index test in up to 20% of disease-negative participants	**B. Disease-negative** • **Yes** - if at least 80% of benign diagnoses were reached by histology and up to 20% were reached by clinical follow-up for a minimum of 3 months following the index test • **No** - if more than 20% of benign diagnoses were reached by clinical follow-up for a minimum of 3 months following the index test or if clinical follow-up period was less than 3 months • **Unclear** - if the method of final diagnosis was not reported for any participant with benign or non-melanoma diagnosis
2. Were the reference standard results interpreted without knowledge of the results of the index test? Please score this item for all studies even though histopathology interpretation is usually conducted with knowledge of the clinical diagnosis (from visual inspection or dermoscopy or both). We will deal with this by not including the response to this item in the 'Risk of bias' assessment for these tests. For reviews of all other tests, this item will be retained	• **Yes** - if the reference standard diagnosis was reached blinded to the index test result • **No** - if the reference standard diagnosis was reached with knowledge of the index test result • **Unclear** - if blinded reference test interpretation was not clearly reported
Could the reference standard, its conduct, or its interpretation have introduced bias? **For visual inspection/dermoscopy evaluations** 1. If answer to question 1 'Yes' 2. If answer to question 1 'No' 3. If answer to question 1 'Unclear' **For all other tests** 1. If answers to questions 1 and 2 'Yes' 2. If answers to questions 1 or 2 'No' 3. If answers to questions 1 or 2 'Unclear'	**For visual inspection/dermoscopy evaluations** 1. Risk is low 2. Risk is high 3. Risk is unclear **For all other tests** 1. Risk is low 2. Risk is high 3. Risk is unclear
Reference standard 3. Concern about applicability	
1. Are index test results presented separately for each component of the target condition (i.e. separate results presented for those with invasive melanoma, melanoma in situ, lentigo maligna, severe dysplasia, BCC, and cSCC)?	• **Yes -** if index test results for each component of the target condition can be disaggregated • **No -** if index test results for the different components of the target condition cannot be disaggregated • **Unclear** - if not clearly reported
2. Expert opinion (with no histological confirmation) was not used as a reference standard 'Expert opinion' means diagnosis based on the standard clinical examination, with no histology or lesion follow-up ***do not complete this item for teledermatology studies	• **Yes** - if expert opinion was not used as a reference standard for any participant • **No** - if expert opinion was used as a reference standard for any participant • **Unclear** - if not clearly reported
3. Was histology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	• **Yes -** if histology interpretation was reported to be carried out by an experienced histopathologist or dermatopathologist • **No -** if histology interpretation was reported to be carried out by a less experienced histopathologist • **Unclear** - if the experience/qualifications of the pathologist

(*Continued*)

	were not reported
Is there concern that the target condition as defined by the reference standard does not match the review question? 1. If answers to all questions 1, 2, and 3 'Yes' 2. If answers to any 1 of questions 1, 2, or 3 'No' 3. If answers to any 1 of questions 1, 2, or 3 'Unclear' ***For teledermatology studies only** 1. If answers to all questions 1 and 3 'Yes' 2. If answers to questions 1 or 3 'No' 3. If answers to questions 1 or 3 'Unclear'	1. Concern is low 2. Concern is high 3. Concern is unclear ***For teledermatology studies only** 1. Concern is low 2. Concern is high 3. Concern is unclear
Flow and timing 4. Risk of bias	
1. Was there an appropriate interval between index test and reference standard? **A.** For histopathological reference standard, was the interval between index test and reference standard ≤ 1 month? **B.** If the reference standard includes clinical follow-up of borderline/benign-appearing lesions, was there at least 3 months' follow-up following application of index test(s)?	**A** • **Yes** - if study reports ≤ 1 month between index and reference standard • **No** - if study reports > 1 month between index and reference standard • **Unclear** - if study does not report interval between index and reference standard **B** • **Yes** - if study reports ≥ 3 months' follow-up • **No** - if study reports < 3 months' follow-up • **Unclear** - if study does not report the length of clinical follow-up
2. Did all participants receive the same reference standard?	• **Yes** - if all participants underwent the same reference standard • **No** - if more than 1 reference standard was used • **Unclear** - if not clearly reported
3. Were all participants included in the analysis?	• **Yes** - if all participants were included in the analysis • **No** - if some participants were excluded from the analysis • **Unclear**- if not clearly reported
4. **For within-person comparisons of index tests** • Was the interval between application of index tests ≤ 1 month?	• **Yes** - if study reports ≤ 1 month between index tests • **No** - if study reports > 1 month between index tests • **Unclear** - if study does not report the interval between index tests
Could the participant flow have introduced bias? **For non-comparative and between-person comparison studies** 1. If answers to questions 1, 2, and 3 'Yes' 2. If answers to any 1 of questions 1, 2, or 3 'No' 3. If answers to any 1 of questions 1, 2, or 3 'Unclear' **For within-person comparative studies** 1. If answers to all questions 1, 2, 3, and 4 'Yes' 2. If answers to any 1 of questions 1, 2, 3, or 4 'No'	**For non-comparative and between-person comparison studies** 1. Risk is low 2. Risk is high 3. Risk is unclear **For within-person comparative studies** 1. Risk is low 2. Risk is high 3. Risk is unclear

(*Continued*)

3. If answers to any 1 of questions 1, 2, 3, or 4 'Unclear'	

BCC: basal cell carcinoma; **cSCC**; cutaneous squamous cell carcinoma

Appendix 9. Summary study details: in-person evaluations

Study Position on clinical pathway [a,b] Outcomes reported	Study type Country Setting	Inclusion criteria	Number-participants/ lesions	Index tests (algorithm) Diagnostic approach	Threshold	Observer qualification (number) Experience	Reference standard Final diagnoses Prevalence (invasive melanoma or atypical intraepidermal melanocytic variants)	Exclusions
Limited prior testing (position 2 on clinical pathway)								
Grimaldi 2009 Pathway: clear MEL	WPC P-CS Italy Primary	Cutaneous PSL requiring confirmation of diagnosis by teledermatology	197/235	VI (no algorithm) Dermoscopy (no algorithm) In-person (single)	Subjective impression ("suspicious for malignancy")	GP (n = 13) Assumed to be low (expertise NR; simple protocols for diagnosis provided for study purposes)	Histology/ clinical FU (6 months) MEL 5; BCC 0; BN 230 (NR) 20%	None reported
Menzies 2009 Pathway: clear MEL Any	WPC P-CS Australia Primary	PSL that would be biopsied or referred on after routine naked eye examination	NR/374	VI (no algorithm) Dermoscopy (no algorithm) In-person (single)	Subjective impression ("correct diagnosis of melanoma")	GP (n = 62) Assumed to be low (trained for study; required history of excision or referral of ≥ 10 pigmented skin lesions over	Histology/ clinical FU (3-6 months)/ expert dx MEL 32; BD 2; BN 323; Unknown 9 4%	6 BCC and 2 BD excluded by study authors, 43 excluded as both VI + dermoscopic diagnoses not available

(*Continued*)

						the previous 12-month period but no prior dermoscopy use)		
Walter 2012 Pathway: clear MM MEL Any	BPC RCT UK Primary	Any suspicious PSL that could not immediately be diagnosed as benign	654/792 (control arm only)	VI (7-point) Siascope (iv arm) In-person (single)	7PCL: ≥ 3	GP (n = 28) Nurse practitioner (n = 2) Low (excluded if specialist dermatology training)	Histology/clinical FU (3-6 months)/expert dx Control group only: MM 16; MiS 2 BCC 4; SK 20; DF 2; lentigo 5; "benign" 686; unknown 10 6%	19 (5 due to violation of recruitment criteria or discontinued protocol; 1 died; 4 did not attend for dermatology assessment; 2 missing histology; 7 not clearly accounted for)
Limited prior testing (selected for excision) (position 3 on clinical pathway)								
Collas 1999 Pathway - unclear MEL	NC P-CS France Mixed (private/hospital)	PSL undergoing excision by dermatologists in private practice, and by hospital dermatologists	353/353	VI (1. no algorithm; 2. own new algorithm) In-person	1. subjective impression 2. ≥ 1 of 3 characteristics present	Dermatologist (n = NR; exp NR) Single observer	Histology MEL 38 BN 249; other pigmented 55 38/353; 11%	None reported
Gachon 2005 Pathway - clear	NC P-CS France Private	Melanocytic skin lesions removed for any reason	NR/4036	VI (no algorithm) In-person; single	Subjective impression ("considered suspicious")	Dermatologists (135/200) Exp NR	Histology MM 113; MiS 36 BN 3887 149/4036; 4%	None reported
McGovern 1992 Pathway - clear	WPC-algs P-CS USA Community (Army Medical Center	PSL (> 10 mm) excised to rule out dysplasia, MiS or MM	179/237	VI (7-point; (A)BCD) In-person; single	7-point: ≥ 2, ≥ 3, ≥ 4 characteristics present (A)BCD: ≥ 1, ≥ 2, ≥	NR (presume dermatologist) Exp NR	Histology MM 6; MiS 6 BCC 4; SK 32; BN 138; AK 6; other	32 lesions unaccounted for; 13 excluded due to lesion size of

(*Continued*)

	Derm-Clinic)				3 characteristics present		45 12/205; 6%	≤ 8 mm. 192 evaluated for ABCD and 3-point; 205 evaluated for 7-point
Referred for further assessment (position 4 on clinical pathway)								
Barzegari 2005 Pathway - clear MEL	WPC NR-CS Iran Secondary	PSL ≤ 15 mm diameter referred to dermatology clinic for diagnostic evaluation or cosmetic reasons	91/122	VI (no algorithm) In-person (consensus diagnosis of 2)	Melanoma likely/ melanoma possible	Mixed (n = 2; 1 attending dermatologist and a third year dermatology resident)	Histology MM 3; MiS 3 SK 2; AK 1; BN 106; DF 7 6/122; 5%	None reported
Stanganelli 2000 Pathway - clear MEL Any	WPC R-CS Italy Specialist clinic	PSL referred by dermatologists and GPs either for presurgical assessment or consultation	NR/3372	VI (ABCD) Dermoscopy (no algorithm) In-person (single)	NR Subjective impression	NR (assumed dermatologist: described as one of the co-authors; n = 1)	Histology/ registry FU MEL 55 BCC 43; BN 3274 55/3372; 2%	None reported
Referred for further assessment (selected for excision) (position 5 on clinical pathway)								
Benelli 1999 Pathway - unclear MEL	WPC P-CS Italy Secondary	All PSL observed and excised at the Dermatologic Surgery Department	NR/401	1. VI (ABCDE) 2. Dermoscopy (7FFM) In-person	1. ≥ 1 characteristic present; ≥ 2 characteristics present; ≥ 3 characteristics present; ≥ 4 characteristics present; all 5 characteristics present 2. Score ≥ 2	Dermatologist (n = 2; exp NR) Consensus of 2	Histology MM 54; MiS 6 BCC 1 BN 337; LS 5; SK 1 60/401; 15%	None reported
Bono 2002a Pathway -	WPC P-CS	PSL with a more or less	298/313	VI (no algorithm)	VI: subjective impres-	Surgical oncologist (n =	Histology MM 55;	None reported

(*Continued*)

clear MEL	Italy Specialist clinic	important suspicion for MM on VI and/or dermoscopy		Dermoscopy (no algorithm) In-person	sion Dermoscopy: ≥ 1 characteristic present	4; high) Single observer	MiS 11 BCC 6; 8 SK; 3 SN; BN 230 66/313; 21%	
Bono 2002b Pathway - clear MEL	WPC P-CS Italy Specialist clinic	PSL ≤ 6 mm requiring surgical biopsy for diagnosis based on clinical or dermoscopic suspicion of MM	157/161	VI (no algorithm) Dermoscopy (no algorithm) In-person	VI: subjective impression Dermoscopy: ≥ 1 characteristic present	Surgical oncologist (n = 2; high) Single observer	Histology MM 10; MiS 3 BCC 2; SK 4; SN 5; BN 124 13/161; 8%	None reported
Bono 2006 Pathway - clear MEL	WPC R-CS Italy Specialist clinic	PSL ≤ 3mm undergoing excision due to a more or less important suspicion for MM on VI and/or dermoscopy	204/206	VI (no algorithm) Dermoscopy (Menzies) In-person	VI: subjective impression Dermoscopy: NR	NR; assumed surgical oncologist as per Bono 2002a; Bono 2002b (n = 4; exp NR) Single observer	Histology MM 19; MiS 4 SN 3; BN 169; Other 11 23/206; 11%	None reported
Carli 2002a Pathway - unclear MEL	WPC R-CS Italy Secondary	Clinically equivocal and suspicious PSL subjected to excisional biopsy at the Institute of Dermatology	NR/256	1. VI (no algorithm) 2. Dermoscopy (pattern) In-person (dermoscopy, image-based)	Subjective impression	Dermatologist (n = 2; high exp - "extensive experience in both clinical and dermoscopic diagnosis") Consensus of 2	Histology MM 40; MiS 14 BCC 5 BN 177; SN 16; SK 4 54/256; 21%	None reported
Cristofolini 1994 Pathway - unclear MEL	WPC P-CS Italy Secondary	Patients with PSL presenting during a campaign for the early diagnosis	NR/220	1. VI (ABCDE) 2. Dermoscopy (pattern) In-person	1. ≥ 2 characteristics present 2. ≥ 1 characteristic present	Dermatologist (n = 4; high exp: dermatologists had all been trained	Histology MEL 33 BCC 0 BN 181; SK 4; 2 thrombosed	None reported

(*Continued*)

		of cutaneous melanoma at the Dermatology Department				in the recognition of pigmented lesions) Unclear observer interpretation	angioma 33/220; 15%	
Cristofolini 1997 Pathway - unclear MEL	WPC-algs NR-CS Italy Secondary	Patients with small and flat common and atypical PSL recruited during a health campaign for the early diagnosis of melanoma; all underwent skin biopsy	176/176	VI (ABCD) In-person	NR	Dermatologist (n = 3; high experience) Consensus of 3	Histology MEL 35 BN 141 35/176; 20%	None reported
Ek 2005 Pathway - clear MEL Any	NC P-CS Australia Specialist clinic	Lesions excised for which malignancy could not be excluded	1223/2582	VI (no algorithm) In-person	Subjective impression	Plastic surgeon (n = 4 or 5; mixed experience; 3 consultants, 1 plastic surgery trainee (usually 1st year, on 6-month rotation) and a clinical assistant) Unclear	Histology MEL 23 BCC 1214; SCC 517; BD 188; SK 63; 577 other BN (including 330 solar keratosis) 23/2582; 1%	Incomplete or incorrectly entered proformas were excluded - 79 participants with 96 lesions
Green 1991 Pathway - clear MEL	NC NR-CS Australia Secondary	PSL for excision	81/89	VI (no algorithm) In-person	Subjective impression	NR (n = NR; exp NR "in the majority of cases a surgeon or a dermatologist") Single	Histology MEL 5 BCC 2; SK 7; BN 54; Other 2 5/70; 7%	19/89 lesions excluded (number of participants not reported) due to incom-

(*Continued*)

						observer		plete clinical and histology records
Langley 2001 Pathway - unclear MEL	NC P-CS USA Specialist clinic	Patients with lesions scheduled for excision at the pigmented lesion clinic to either remove atypical naevi or to rule out melanoma or for cosmetic reasons	NR/38	VI (no algorithm) In-person	NR	NR (presume dermatologist; n = NR; exp NR) Unclear	Histology MM 3; MiS 3 BN 32 6/38; 16%	None reported
Morales Callaghan 2008 Pathway - unclear MEL	WPC P-CS Spain Secondary	Randomly selected melanocytic lesions; melanocytic on both clinical and dermoscopic criteria	166/200	1. VI (no algorithm) 2. Dermoscopy (no algorithm) In-person	NR	Dermatologist (n = 2; high exp - "experience in dermoscopy") Consensus of 2	Histology MEL 6 BN 184; SN 1; Other 9 6/200; 3%	None reported
Morton 1998a (high exp), Morton 1998b (mod exp), and Morton 1998c (low exp) Pathway - clear MEL	NC R-CS UK Specialist clinic	Patients referred by their GP to the clinic	NR/1999	VI (no algorithm) In-person	NR	Dermatologist (n = 2; high); Dermatology senior registrar (n = 1; moderate); Dermatology registrar (n = 1; low) SIngle observer per lesion	Histology MM 104; MiS 24 BN 1871 High exp: 69/763; 9% Moderate exp: 31/567; 5% Low exp: 28/669; 4%	None reported
Thomas 1998 Pathway - unclear MEL	NC CCS France Secondary	All cases of melanoma and a nonselected consecu-	NR/1140	VI (ABCDE) In-person	≥ 1 characteristic present ≥ 2 charac-	Dermatologist (n = 2; high exp: described as	Histology MEL 460 BCC 8 BN 638; SN	None reported

(*Continued*)

		tive group of "non-melanoma" PSL			teristics present ≥ 3 characteristics present ≥ 4 characteristics present all 5 characteristics present	"trained dermatologists") Single observer	2; Other 13 460/1140; 40%	
Unlu 2014 Pathway - unclear MEL	WPC-algs R-CS Turkey Specialist clinic	Melanocytic lesions excised at Department of Dermatology Pigmented Lesion Clinic	115/115	1. VI (no algorithm) 2. Dermoscopy (7-point; 3-point; CASH; ABCD) In-person	1. subjective impression 2. score ≥ 3; ≥ 2 characteristics present; score ≥ 8; score > 5.44	NR (presume dermatologist; n = 1 for VI; n = 3 for dermoscopy; Exp NR for VI) Single observer (VI); consensus of 3 (dermoscopy)	Histology MEL 24 BN 91 24/115; 21%'	None reported
Zaumseil 1983 Pathway - unclear MEL	NC NR-CS Germany Secondary	Skin lesions undergoing excision	NR/7063	VI (no algorithm) In-person	Subjective impression	NR (n = NR; exp NR) Single observer	Histology MEL 337 Not melanoma 6726 (dx listed only for FPs) 337/7063; 5%	None reported
Equivocal referred for further assessment (selected for excision) (position 5* on clinical pathway)								
Dummer 1993 Pathway - clear MEL	WPC P-CS Germany	Patients with melanocytic skin lesions difficult to diagnose clinically	NR/771	VI (no algorithm) Dermoscopy (pattern) In-person (image-based for dermoscopy)	NR	NR assume dermatologist (assumed) (n = 2; exp NR) Single observer	Histology MM 19; MiS 4 SK 4; BN 706; BN NML 32; other 6 23/771; 3%	53 non-melanocytic lesions not included in the final analysis (no melanomas present in this group)

(*Continued*)

Soyer 1995 Pathway - clear MEL	WPC NR-CS Austria	PSL difficult to diagnose on clinical grounds alone	NR/159	VI (no algorithm) Dermoscopy (pattern) In-person	NR	Dermatologist (n = 2; exp high; "the examination was performed by a dermatologist expert in dermoscopy") Single observer	Histology MM 50; MiS 15 BCC 3; SK 18; AK 4; BN 61; other 7 65/159; 41%	None reported
Steiner 1987 Pathway - unclear MEL	P-CS Austria Specialist clinic	Small (< 10 mm) diagnostically equivocal PSL; no absolute agreement on clinical diagnosis among investigating clinicians at a pigmented lesion clinic	NR/318	1. VI (no algorithm) 2. Dermoscopy (pattern) In-person	Subjective impression	Dermatologists (n = 3; high exp: "experienced dermatologists") Consensus diagnosis of 3 observers	Histology MM 49; MiS 24 BCC 20 BN 143; SK 20; lentigo simplex and nevoid lentigo 19; other 15 73/318; 23%	None reported

[a] positions on the clinical pathway described in Figure 3.
[b] clear or unclear position on the clinical pathway.
AHM: atypical melanocytic naevi; **AK**: actinic keratosis; **BCC**: basal cell carcinoma; **BD**: Bowen's disease; **BN**: benign naevi; **BNM**: benign non-melanocytic; **BPC**: between-person comparison (of tests); **CCS**: case control study; **CS**: case series; **cSCC**: cutaneous squamous cell carcinoma; **DF**: dermatofibroma; **dx**: diagnosis; **ELM**: epiluminescence microscopy; **Exp**: experience; **FP**: false-positive; **FU**: follow-up; **GP**: general practitioner; **LS**: lentigo simplex; **MEL**: invasive melanoma or atypical intraepidermal melanocytic variants; **MM**: malignant (invasive) melanoma; **MiS**: melanoma in situ (or lentigo maligna); **NC**: noncomparative; **NR**: not reported; **P**: prospective; **PLC**: pigmented lesion clinic; **PSL**: pigmented skin lesion; **R**: retrospective; **RCT**: randomised controlled trial; **SCC**: squamous cell carcinoma; **SK**: seborrhoeic keratosis; **SN**: Spitz naevi; **VI**: visual inspection; **WPC**: within-person comparison (of tests); **WPC-algs**: within-person comparison (of algorithms); **7FFM**: seven features for melanoma; **7PCL**: seven-point checklist

Appendix 10. Summary QUADAS: in-person evaluations

	Studies clearly placed on clinical pathway		Studies not clearly placed on clinical pathway	
Pathway [a,b]	**Risk of bias**	**Concerns about applicability**	**Risk of bias**	**Concerns about applicability**
Limited prior testing (position 2 on clinical pathway)				
Studies	**N = 3**; Grimaldi 2009; Menzies 2009; Walter 2012		**N = 0**	
Participant selection	Low (3/3)	High (2/3) Unclear (1/3) Inclusion of multiple lesions per participant (Grimaldi 2009; Walter 2012); patient numbers NR (Menzies 2009)	-	-
Index test	Low (1/3) Unclear (2/3) Lack of clear pre-specification of threshold (Grimaldi 2009; Menzies 2009)	Low (1/3) High (2/3) Lack of description of diagnostic threshold (Grimaldi 2009; Menzies 2009). Non-expert test interpretation (Menzies 2009; Walter 2012); not clear in Grimaldi 2009	-	-
Reference standard	High (3/3) < 80% of disease-negative participants had histological or clinical follow-up reference standard	High (2/3) Unclear (1/3) Expert diagnosis as reference standard (Menzies 2009; Walter 2012); unclear histopathologist expertise (3/3)	-	-
Flow and timing	High (3/3) Mixed reference standards (3/3); participant exclusions (Menzies 2009; Walter 2012); all unclear on index to reference interval	-	-	-
Limited prior testing (selected for excision) (position 3 on clinical pathway)				
Studies	**N = 2**; Gachon 2005; McGovern 1992		**N = 1**; Collas 1999	

(*Continued*)

Participant selection	Low (1/2) Unclear (1/2) Unclear exclusion criteria (1/2; Gachon 2005).	High (2/2) Restriction to melanocytic (1/2; Gachon 2005) or primarily excised lesions (2/2); multiple lesions per participant (1/2; McGovern 1992); number participants NR (1/2; Gachon 2005)	Unclear (1/1) Participant sampling not described; exclusion criteria NR	High (1/1) Excised only included
Index test	Unclear (1/2) High (1/2) Lack of clear pre-specification of the threshold (1/2; Gachon 2005) or testing of multiple thresholds (1/2; McGovern 1992)	High (1/2) Unclear (1/2) Lack of threshold detail (1/2; Gachon 2005); unclear description of observer expertise (2/2)	Low (1/1)	Unclear (1/1) Observer expertise not described
Reference standard	Low (2/2)	Low (1/2) Unclear (1/2) Lack of description of histopathology expertise (1/2; Gachon 2005)	Low (1/1)	Unclear (1/1) Histology expertise not described (histologically analysed by different private and hospital pathologists and reviewed by one of the study authors)
Flow and timing	High (1/2) Unclear (1/2) Participant exclusions (1/2; McGovern 1992); unclear reference interval (2/2).	-	Low (1/1)	-
Referred for further assessment (position 4 on clinical pathway)				
Studies	**N = 2**; Barzegari 2005; Stanganelli 2000		**N = 0**	
Participant selection	Low (2/2)	High (2/2) Included excisions for cosmetic reasons (1/2; Barzegari 2005), or multiple lesions per participant (2/2)	-	-
Index test	Low (1/2) Unclear (1/2) Lack of clear pre-speci-	High (1/2) Unclear (1/2) Consensus result (1/2;	-	-

(*Continued*)

	fication of the threshold (Barzegari 2005)	Barzegari 2005); insufficient threshold detail (1/2; Barzegari 2005); observer expertise not clear (2/2)		
Reference standard	Low (1/2) High (1/2) < 80% of disease-negative participants had histological or clinical follow-up reference standard (Stanganelli 2000)	Unclear (2/2) Lack of description of histopathology expertise (2/2)	-	-
Flow and timing	High (1/2) Unclear (1/2) Unclear reference interval (2/2); use of different reference standards (1/2; Stanganelli 2000)	-	-	-
Referred for further assessment (selected for excision) (position 5 on clinical pathway)				
Studies	**N = 6**; Bono 2002a; Bono 2002b; Bono 2006; Ek 2005; Green 1991; Morton 1998a; Morton 1998b; Morton 1998c [b]		**N = 9**; Benelli 1999; Carli 2002b; Cristofolini 1994; Cristofolini 1997; Langley 2001; Morales Callaghan 2008; Thomas 1998; Unlu 2014; Zaumseil 1983	
Participant selection	Low (2/6) High (2/6) Unclear (2/6) Inappropriate (2/6; Bono 2002a; Ek 2005) or unclear (2/6; Green 1991; Morton 1998a; Morton 1998b; Morton 1998c) exclusions; consecutive recruitment not reported (1/6; Green 1991)	High (6/6) Unrepresentative (6/6) participants; all excised. Multiple lesions per participant (2/6; Ek 2005; Green 1991) or number of participants NR (Morton 1998a; Morton 1998b; Morton 1998c)	High (4/9) Unclear (5/9) Inappropriate exclusions (4/9) due to restriction to melanocytic only (Morales Callaghan 2008; Unlu 2014) , disagreement on histology (Zaumseil 1983). Use of case-control type design (1/9; Thomas 1998). Unclear participant sampling (6/9; Benelli 1999; Carli 2002b; Cristofolini 1994; Cristofolini 1997; Langley 2001; Zaumseil 1983).	High (9/9) Inclusion of only excised lesions (9/9). Multiple lesions per participant (2/9; Langley 2001; Morales Callaghan 2008); number of participants not reported (6/9; Benelli 1999; Carli 2002b; Cristofolini 1994; Cristofolini 1997; Thomas 1998; Zaumseil 1983)
Index test	Low (3/6) Unclear (3/6) Pre-specification of threshold not reported	High (6/6) All clinically applicable application of test. No threshold details (6/6).	Low (2/9) High (2/9) Unclear (5/9) Threshold not prespeci-	Low (1/9) High (7/9) Unclear (1/9) Test application not clin-

(*Continued*)

	(Ek 2005; Green 1991; Morton 1998a; Morton 1998b; Morton 1998c)	Observer experience unclear (3/6; Bono 2006; Ek 2005; Green 1991).	fied (2/9; Benelli 1999; Thomas 1998) or not clear whether prespecified (Carli 2002b; Cristofolini 1997; Langley 2001; Morales Callaghan 2008; Unlu 2014).	ically applicable (4/9; Benelli 1999; Carli 2002b; Cristofolini 1997; Morales Callaghan 2008) or not clear (Cristofolini 1994; Langley 2001). No threshold detail (5/9; Carli 2002b; Langley 2001; Morales Callaghan 2008; Unlu 2014; Zaumseil 1983)
Reference standard	Low (5/6) High (1/6) Inadequate reference standard (1/6; Green 1991)	Low (1/6) High (1/6) Unclear (4/6) Expert diagnosis used (1/6; Green 1991). Lack of description of histopathology expertise (5/6; all except Morton 1998a; Morton 1998b; Morton 1998c)	Low (9/9)	Low (2/9) High (1/9) Unclear (6/9) Use of expert diagnosis (1/9; Langley 2001). Histopathology expertise not reported (7/9; Benelli 1999; Carli 2002b; Cristofolini 1994; Cristofolini 1997; Langley 2001; Morales Callaghan 2008; Zaumseil 1983)
Flow and timing	High (2/6) Unclear (4/6) Index to reference interval not reported (5/6; Bono 2002a; Bonon 2002b; Bono 2006; Green 1991; Morton 1998a; Morton 1998b; Morton 1998c). Participant exclusions due to incomplete data (2/6; Ek 2005; Green 1991)	-	Low (3/9) Unclear (6/9) Interval to reference standard not reported (6/9; Benelli 1999; Cristofolini 1994; Langley 2001; Thomas 1998; Unlu 2014; Zaumseil 1983)	-
Equivocal referred for further assessment (selected for excision) (position 5* on clinical pathway)				
Studies	**N = 2**; Dummer 1993; Soyer 1995		**N = 1**; Steiner 1987	
Participant selection	Unclear (2/2) Unclear sampling methods (2/2); Unclear exclusions (1/2; Soyer 1995)	High (1/2) Unclear (1/2) Participants not representative (1/2; Dummer 1993) or unclear (1/2; Soyer 1995). Number of	Unclear (1/1) Participant sampling not described; exclusion criteria not reported	High (1/1) Restricted to small < 10 mm pigmented skin lesions; all excised

(*Continued*)

		participants NR (2/2)		
Index test	Unclear (2/2) Pre-specification of threshold not reported (2/2)	High (2/2) No threshold details (2/2). Observer experience unclear (1/2; Dummer 1993)	Unclear (1/1) Pre-specification of threshold NR	High (1/1) Consensus decision reported and no threshold detail
Reference standard	Low (2/2)	Unclear (2/2) Lack of description of histopathology expertise (2/2)	Low (1/1)	Unclear (1/1) Histology expertise not described
Flow and timing	High (1/2) Unclear (1/2) Participant exclusions (1/2; Dummer 1993). Index to reference interval not reported (2/2)	-	Low (1/1)	-

[a] positions on the clinical pathway described in Figure 3.
[b]The study by Morton et al is considered as a single study for quality assessment purposes but as three studies (Morton 1998a; Morton 1998b; Morton 1998c) for the analyses due to the reporting of three separate cohorts of participants
NR: not reported

Appendix 11. Summary study details: image-based evaluations

Study Position on pathway [a,b] **Outcomes reported**	**Study type Country Setting**	**Inclusion criteria**	**Numberparticipants/lesions**	**Index tests (algorithm) Diagnostic approach**	**Threshold**	**Observer qualification (number) Experience**	**Reference standard Final diagnoses Prevalence (MEL)**	**Exclusions**
Limited prior testing (with selection on reference standard) (position 3 on clinical pathway)								
Bourne 2012 Path-	WPC-tests R-CS Aus-	All skin lesions excised to exclude skin cancer (and 3 examples common lesions assessed as clearly be-	46/50	VI (no algorithm) Dermoscopy (3-point; Menzies; BLINCK	NR	GP (n = 3) Clini-	Histology/ clinical	5 non-pig-

(*Continued*)

way - clear	tralia Primary	nign and not biopsied)		(excluded)) Image-based (blinded)		cal nurse (n = 1) Mixed experience "varying levels of dermatoscopic experience" Average	FU/expert dx MM 1; MiS 8 BCC 6; SK 5; BN 11; other 19 9/45; 20%	mented specimens (not further identified) in the set of 50 were excluded from dermoscopic evaluations
Rosenda 2011 Pathway - unclear	NC R-CS Australia Primary	PSL submitted for histology from the primary care skin cancer practice of one study author	389/463	1. VI (no algorithm) 2. Dermoscopy (pattern)	1. Subjective impression 2. Both characteristics present	Dermatologist (n = 1) Image-based; high experience (confirmed by study author); single observer	Histology MM 9; MiS 20 BCC 72; SCC 5 BN 217; BD 18; AK 14*; BNM 140 *considered malignant by study authors 29/463; 6%	3 poor-quality images excluded
Referred for further assessment (position 4 on clinical pathway)								
Stanganelli 2005	WPC R-CS Italy	Melanocytic lesions referred to Skin Cancer Unit for clinical and dermo-	NR/477	VI (no algorithm) Dermsocopy (no	NR	Dermatol-	Histology/	None re-

(*Continued*)

Pathway - clear MEL	Specialist clinic	scopic evaluation		algorithm) Image-based (average)		ogist (n = 3); GP (n = 3) Dermatologists - high experience ("2 years dermoscopy experience"); experience NR for GPs, assumed low	registry FU MEL 31 BN 103 31/134; 23%	ported
Referred for further assessment (with selection on reference standard) (position 5 on clinical pathway)								
Benelli 2001 Pathway - unclear	WPC R-CS Italy Training images	Slides of PSL selected for evaluation during a training course on dermoscopy. Lesions not located on head, palms or soles	NR/49	1. VI (ABCDE) 2. Dermoscopy (7FFM)	1. ≥ 3 & ≥ 2 2. ≥ 2	Expert author (n = 1); dermatologists (n = 65) Image-based; single author - high experience; Average result for dermatol-	Histology MM 10, MiS 2 BCC 2 BN 25, SN 5, SK 3, other 2 (1 missing) 12/50; 24%	None reported

(*Continued*)

						ogist group; experience NR		
Carli 2002b Pathway - unclear	WPC R-CS Italy Secondary	Clinically suspicious or equivocal PSL undergoing excision for diagnostic purposes; all ≤ 14 mm diameter	NR/57	1. VI (NR) 2. Dermoscopy (NR)	NR	Dermatologists (n = 2) Image-based; high experience ("with experience in the field of PSL"); consensus of 2	Histology MM 6, MiS 5 BCC 10 BN 31, SK 1; other 4 11/57; 19%	4 "not evaluables" excluded (1 MM, 3 benign)
Dolianitis 2005 Pathway - unclear	WPC CCS Multi-centre Training images	Melanocytic skin lesions selected from a collection of dermoscopic images belonging to one study author	NR/40	1. VI (no algorithm) 2. Dermoscopy (pattern analysis; Menzies criteria; 7-point; ABCD)	1. Subjective impression 2. Subjective impression; NR; NR; > 4.75	Dermatologists (n = 16); dermatology trainees (n = 16); GPs (n = 35) Image-based; mixed experience ("range of experience	Histology (n = 39); Expert diagnosis (n = 1) MM 18, MiS 2 BN 12; SN 3; other 4 20/20; 50%	None reported; poor-quality images exclusion criterion

(*Continued*)

						levels with assessment of skin lesions"); average result		
Pizzichet 2004 Pathway - unclear	WPC R-CS USA/Italy Secondary	Clinical and/or dermoscopic hypomelanotic (extent of pigmentation ≤ 30%) and amelanotic skin lesions	151/151	1. VI (no algorithm) 2. Dermoscopy (pattern)	Subjective impression	NR (presume dermatologist; n = 1) Image-based; experience NR; single observer	Histology AHM 34, MiS 5 BCC 25, SCC 5 BN 47, SN 5, SK 8, other 18 39/108; 36% (analysed)	23 lesions excluded due to image quality; further 43 lesions were not available for evaluation by clinical images ("mainly benign melanocytic lesions")
Stanganelli 1998a Pathway - unclear	WPC R-CS Italy Training images	PSL images selected from computerised files of the skin cancer clinic	NR/30	1. VI (no algorithm) 2. Dermoscopy (no algorithm)	NR	Dermatologists (n = 20) Image-based; experience NR ("expe-	Histology MEL 10 BCC 4 BN 10, SK 3, other 3 10/30; 33%	None reported

(*Continued*)

						rience in ELM but (with) no formal training"); average		
Winkelmann 2016 Pathway - unclear	WPC CCS Unclear Training images	Selected images previously analysed by MSD-SLA	NR/12	1. VI (no algorithm) 2. Dermoscopy (no algorithm)	NR	Dermatologists (n = 70) Image-based; experience NR; average	Histology MM 3; MiS 2 BN 7 5/12; 42%	None reported
Equivocal referred for further assessment (with selection on reference standard) (position 5* on clinical pathway)								
Carli 2003a Pathway - unclear	WPC R-CS Italy Secondary	Clinically difficult to diagnose or equivocal melanocy lesions randomly selected from image database; all melanon < 1 mm	NR/200	1. VI (no algorithm) 2. Dermoscopy (own choice)	Subjective impression	Dermatology registrar (n = 2); dermatologists (senior experts n = 2; practicing dermatologists n = 4)	Histology MM 40; MiS 24 BN 136 64/200; 32%	None reported

(*Continued*)

		thickness				Classed as high experience (both dermatologists and registrars "formally trained in dermoscopy; Average result		
de Giorgi 2012 Pathway - unclear	WPC R-CS Italy Secondary	Pigmented melanocy skin lesions ≤ 6 mm diameter excised at dermatology department	NR/103	VI (ABCD)	1. ≥ 2 characteristics present 2. ≥ 3 characteristics present	Dermatologists (n = 3) High experience ("more than 5 years of practice in dermoscopy; consensus of 3	Histology MM 16; MiS 18 BN 69 34/103; 33%	None reported

[a] positions on the clinical pathway described in Figure 3.
[b] clear or unclear position on the clinical pathway.
AHM: amelanotic hypomelanotic melanoma; **AK**: actinic keratosis; **BCC**: basal cell carcinoma; **BD**: Bowen's disease; **BLINCK**: Benign Lonely irregular Nervous Change Known Clues; **BN**: benign naevi; **BNM**: benign non-melanocytic; **BPC**: between-person comparison (of tests); **CCS**: case-control study; **CS**: case series; **cSCC**: cutaneous squamous cell carcinoma; **DF**: dermatofibroma; **dx**: diagnosis; **ELM**: epiluminescence microscopy; **FU**: follow-up; **GP**: general practitioner; **LS**: lentigo simplex; **MEL**: invasive melanoma or atypical intraepidermal melanocytic variants; **MiS**: melanoma in situ (or lentigo maligna); **MM**: malignant (invasive) melanoma; **MSDSLA**: multispectral digital skin lesion analysis device; **NC**: non comparative; **NR**: not reported; **P**: prospective; **PLC**: pigmented lesion clinic; **PSL**: pigmented skin lesion; **R**: retrospective; **RCT**: randomised controlled trial; **SCC**: squamous cell carcinoma; **SK**: seborrhoeic keratosis; **SN**: Spitz naevi; **VI**: visual inspection; **WPC**: within person comparison (of tests); **7FFM**: seven features for melanoma; **7PCL**: seven-point checklist

Appendix 12. Summary QUADAS: image-based evaluations

	Studies clearly placed on clinical pathway		Studies not clearly placed on clinical pathway	
Pathway [a]	**Risk of bias**	**Concerns about applicability**	**Risk of bias**	**Concerns about applicability**
Limited prior testing (with selection on reference standard) (position 3 on clinical pathway)				
Studies	**N = 1**; Bourne 2012		**N = 1**; Rosendahl 2011	
Participant selection	Unclear (1/1) Unclear exclusion criteria (Bourne 2012)	High (1/1) Restriction to primarily excised lesions (1/1)	Low (1/1)	High (1/1) Includes excised lesions only; multiple lesions per participant
Index test	Unclear (1/1) Lack of clear pre-specification of the threshold (Bourne 2012)	High (1/1) Blinded image interpretation and average observer result presented (Bourne 2012); lack of threshold detail (Bourne 2012); unclear description of observer expertise	Unclear (1/1) No clear pre-specification of threshold	High (1/1) Image-based study; no threshold detail
Reference standard	Low (1/1)	High (1/1) Use of expert diagnosis as reference (Bourne 2012) ; lack of description of histopathology expertise (Bourne 2012)	Low (1/1)	Unclear (1/1) Histopathology experience NR
Flow and timing	High (1/1) Use of different reference standards (Bourne 2012) ; participant exclusions (Bourne 2012)	-	High (1/1) Exclusions on image quality Unclear interval between index and reference	-
Referred for further assessment (position 4 on clinical pathway)				
Studies	**N = 1;** Stanganelli 2005		**N = 0**	
Participant selection	Unclear (1/1) Unclear participant sampling across all items (Stanganelli 2005)	High (1/1) Sample restricted to melanocytic lesions (Stanganelli 2005)	-	-

(*Continued*)

		. Patient numbers NR		
Index test	Unclear (1/1) Lack of clear pre-specification of the threshold (Stanganelli 2005)	High (1/1) Average result presented (Stanganelli 2005); insufficient threshold detail (Stanganelli 2005)	-	-
Reference standard	Low (1/1)	Unclear (1/1). Unclear use of expert diagnosis as reference standard (Stanganelli 2005). Unclear histopathology expertise	-	-
Flow and timing	High (1/1) Use of different reference standards (Stanganelli 2005); unclear reference interval	-	-	-
Referred for further assessment (with selection on reference standard) (position 5 on clinical pathway)				
Studies	**N = 0**		**N = 6**; Benelli 2001; Carli 2002b; Dolianitis 2005; Pizzichetta 2004; Stanganelli 1998a; Winkelmann 2016	
Participant selection	-	-	High (3/6) Unclear (3/6) Case-control type design used (3/3; Dolianitis 2005; Stanganelli 1998a; Winkelmann 2016) or unclear design (Benelli 2001; Pizzichetta 2004). Unclear participant sampling (5/6; Benelli 2001; Carli 2002b; Pizzichetta 2004; Stanganelli 1998a; Winkelmann 2016), design unclear (1/6), exclusion criteria not clearly reported (5/6; Benelli 2001; Carli 2002b; Dolianitis 2005; Stanganelli 1998a; Winkelmann 2016)	High (6/6) Excised only included (6/6), amelanotic/ hypomelanotic lesions only (1/6; Pizzichetta 2004). Number participants NR (5/6; Benelli 2001; Carli 2002b' Dolianitis 2005; Stanganelli 1998a; Winkelmann 2016)

(*Continued*)

Index test	-	-	Low (1/6) Unclear (5/6) No clear pre-specification of threshold (5/6; Carli 2002b; Dolianitis 2005; Pizzichetta 2004; Stanganelli 1998a; Winkelmann 2016)	High (6/6) Image-based evaluations (6/6), blinded to all other information (5/6; Benelli 2001; Carli 2002b; Dolianitis 2005; Stanganelli 1998a; Winkelmann 2016), with consensus (1/6; Carli 2002b) or average result (4/6; Benelli 2001; Dolianitis 2005; Stanganelli 1998a; Winkelmann 2016) reported. Threshold not clearly specified (5/6; Carli 2002b; Dolianitis 2005; Pizzichetta 2004; Stanganelli 1998a; Winkelmann 2016). Observer expertise NR (4/6; Dolianitis 2005; Pizzichetta 2004; Stanganelli 1998a; Winkelmann 2016)
Reference standard	-	-	Low (6/6)	High (1/6) Unclear (5/6) Use of expert observer diagnosis (1/6; Dolianitis 2005); expertise of histopathologist not described (6/6)
Flow and timing	-	-	Low (1/6) High (2/6) Unclear (3/6) Lesions excluded from analysis (reason NR) (2/6; Dolianitis 2005; Pizzichetta 2004); different reference standards used (1/6; Dolianitis 2005). Index to reference interval NR (5/6; Benelli 2001, Dolianitis 2005, Pizzichetta 2004, Stanganelli 1998a, Winkelmann 2016).	-

(*Continued*)

Equivocal referred for further assessment (with selection on reference standard) (position 5* on clinical pathway)				
Studies	**N = 0**		**N = 2**; Carli 2003a; de Giorgi 2012	
Participant selection	-	-	High (2/2) Exclusion of difficult to diagnose, including peculiar lesions (1/2; Carli 2003a), histology disagreement (1/2; de Giorgi 2012)	High (2/2) Restriction to melanocytic only (2/2), excised only (2/2). Patient numbers NR (2/2)
Index test	-	-	High (1/2) Unclear (1/2) Multiple thresholds tested (1/2; de Giorgi 2012); no clear threshold specification (1/2; Carli 2003a)	High (2/2) Image-based evaluations (2/2), blinded to all other information (1/2; Carli 2003a), with consensus (1/2; de Giorgi 2012) or average result (1/2; Carli 2003a) reported. Threshold not described (1/2; Carli 2003a)
Reference standard	-	-	Low (2/2)	Low (2/2)
Flow and timing	-	-	Unclear (2/2) Index to reference interval NR (2/2)	-

[a] positions on the clinical pathway described in Figure 3.
NR: not reported

Appendix 13. Summary study details: detection of invasive melanoma alone

Study author **Outcomes reported**	**Study type** **Country** **Setting**	**Inclusion criteria**	**Number-participants/ lesions**	**Index tests (algorithm)** **Diagnostic approach**	**Threshold**	**Observer qualifications (number)** **Experience**	**Reference standard** **Final diagnoses** **Prevalence (MEL)**	**Exclusions**
In-person								

(*Continued*)

Bono 1996	WPC-tests Unclear Italy Specialist clinic	Pigmented skin lesions at the Instituto Nazionale Tumori of Milan	45/54	VI (no algorithm) Single observer	Subjective impression	Plastic surgeon	Histology plus other (31% of benign had expert dx) MM: 18 BN: 25 18/43; 42%	Only 43 lesions had complete clinical and histological information. 11 lesions not surgically removed had only clinical diagnosis (benign) and were not included in the final accuracy analysis
Green 1994	NC NR-CS Australia Secondary	Pigmented lesions for excision	129/164	VI (no algorithm) Single observer	Subjective impression; clinical dx recorded	NR	Histology MM 18; MiS 3 BN 128; misc pigmented lesions including SK, BCC, lentigines 15 18/164; 11%	-
Kopf 1975	NC R-CS USA Specialist clinic	All lesions subject to biopsy at the Oncology Section of the Skin and Cancer Unit	NR/5538	VI (no algorithm) Single observer	No details; "clinical diagnosis"	Oncologist	Histology MM 99 other dx listed only for false-positives 99/5538; 2%	None reported
Krahn 1998	WPC-tests P-CS Germany Secondary	Excised pigmented skin lesions	80/80	VI (no algorithm) Single observer	No details	Dermatologist (assumed)	Histology MM 39 BN 40; SN 1 39/80; 49%	None reported
McGovern 1992	WPC-algs P-CS USA	PSL (> 10 mm) excised to rule out	179/237	VI (7-point; (A)BCD) In-person;	7-point: ≥ 2, ≥ 3, ≥ 4 character-	NR (presume der-	Histology MM 6; MiS	32 lesions unac-

(*Continued*)

	Community	dysplasia, MiS or MM		single	istics present (A)BCD: ≥ 1, ≥ 2, ≥ 3 characteristics present	matologist) experience. NR	6 BCC 4; SK 32; BN 138; AK 6; other 45 6/211; 3%	counted for; 13 excluded due to lesion size of ≤ 8 mm. 192 evaluated for ABCD and 3-point; 205 evaluated for 7-point
Viglizzo 2004	WPC-tests NR-CS Italy Specialist clinic	Pigmented skin lesions examined at the Dermoscopy Service and undergoing excisions; high and medium risk on dermoscopy were selected for excision and 2x2 can be estimated only for melanocytic subgroup	NR/79	VI (no algorithm) Single observer	No details	Dermatologist (assumed)	Histology Melanoma (invasive): 11; MiS: 1 Melanocytic lesion: 57 11/67 16%	None reported
Walter 2012	BPC RCT UK Primary	Any suspicious PSL that could not immediately be diagnosed as benign	654/ 792 (control arm only)	VI (7-point) Siascope (iv arm) In-person (single)	NR	GP (n = 28) Nurse practitioner. (n = 2) Low (excluded if specialist dermatology training)	Histology/ clinical FU (3-6 months)/ expert dx Control group only: MM 16; MiS 2 BCC 4; SK 20; DF 2; lentigo 5; "benign" 686; unknown 10 16/773 2%	19 (5 due to violation of recruitment criteria or discontinued protocol; 1 died; 4 did not attend for dermatology assessment; 2 missing histology; 7 not clearly accounted for)

(*Continued*)

Image-based								
Lorentzen 1999	WPC-tests P-CS Denmark Secondary	Patients with lesions suspicious for CMM referred to outpatients clinic	232/232	VI (no algorithm) (Dermoscopy) Single observer	Subjective impression; clinical diagnosis	Dermatologist	Histology MM 49 "malignant melanoma" BCC 16, SK 12; BN: 137 other: 18 (including SN, BD, and others) 49/232; 21%	Poor-quality index test image 10 cases excluded
Rao 1997	WPC-algs (tests) R-CS USA Private	Patients with atypical melanocytic lesions or suspected early MM	63/72	VI (ABCD) (Dermoscopy) Single observer	Diagnosis of melanoma	Dermatology registrar	Histology MM 21 Atypical melanocytic naevus 51 21/72; 29%	None reported
Scope 2008	NC R-CS New Zealand Industry image database	Images of pigmented skin lesions selected from a database of standardised patient images provided by a New Zealand-based teledermatology company (MoleMap); images were selected on the basis that (1) ≥ 8 clinically atypical naevi were apparent on the back;	12/145	VI (ugly duckling) Single observer	Lesion id as "completely different" or somewhat different from the other moles; (Bx) decision	Dermatologist	Histology or FU MM 5 "malignant melanoma" BN: 140 5/145; 3%	Unacceptable image quality

(*Continued*)

		(2) most of the lesions on the back and all of the atypical naevi had close-up clinical digital images; (3) 1-year FU images (close-up clinical and dermoscopic images) were available to show that lesions considered to be benign were in fact biologically indolent by revealing no change; and (4) the image quality of both the overview and the close-up images were acceptable						
Troyanova 2003	BPC/WPC-tests R-CCS NR Training images (source NR)	Images of pigmented skin lesions selected for a dermoscopy training study	NR/50	VI (no algorithm) (Dermoscopy) Single observer	Subjective impression; dx of melanoma	Dermatologist	Histology MM: 25 "Benign": 25 25/50; 50%	None reported
Westerhoff 2000	WPC-tests R-CCS Australia Training	Clinically atypical pigmented skin lesions;	NR/100	VI (no algorithm) (Dermoscopy)	Subjective impression; dx of melanoma	GP	Histology or FU MM 50 "Benign":50	None reported

(*Continued*)

	images (Specialist unit)	50 invasive melanomas and 50 non-melanomas randomly selected from the Sydney Melanoma Unit PSL image database		Single observer			50/100; 50%	

AK: actinic keratosis; **BCC**: basal cell carcinoma; **BD**: Bowen's disease; **BN**: benign naevi; **BPC**: between person comparison (of tests) ; **Bx**: biopsy; **CCS**: case control study; **CMM**: cutaneous malignant melanoma; **CS**: case series; **DF**: dermatofibroma; **FU**: follow-up; **MEL**: invasive melanoma or atypical intraepidermal melanocytic variants; **MiS**: melanoma in situ (or lentigo maligna); **MM**: malignant melanoma; **NC**: non comparative; **NR**: not reported; **P**: prospective; **PLC**: pigmented lesion clinic; **PSL**: pigmented skin lesion; **R**: retrospective; **RCT**: randomised controlled trial; **SK**: seborrhoeic keratosis; **SN**: Spitz naevi; **VI**: visual inspection; **WPC**: within person comparison (of tests); **WPC-algs**: within-person comparison (of algorithms)

Appendix 14. Summary study details: detection of any skin lesion requiring excision

Study author **Outcomes reported**	**Study type Country Setting**	**Inclusion criteria**	**Numberparticipants/lesions**	**Index tests (algorithm) Diagnostic approach**	**Threshold**	**Observer qualifications (number) Experience**	**Reference standard Final diagnoses Prevalence (MEL)**	**Exclusions**
In-person								
Argenziano 2006	RCT Italy, Spain Primary	Patients asking for screening or exhibiting ≥ 1 skin tumours as seen during routine physical examination (patient-finding screening) Participating PCPs randomised to either VI alone or VI	NR/85	VI (ABCD) Dermoscopy (3-point checklist) In person (single observer)	Subjective impression; dx of malignancy	GPs (n = 37) All trained in ABCD rule	Histology MEL 6 BCC 37; SCC 10 benign 32 53/85; 62%	Only those participants who were considered to have lesions

(*Continued*)

		+ dermoscopy; only excised lesions can be included for each arm						sug-gestive of skin cancer had histol-ogy and could be in-cluded; rest had expert diag-nosis (making full dataset ineli-gible for this review)
Chang 2013	NC R-CS Taiwan Sec-ondary	Po-tentially malignant biopsied or excised skin lesions (nontu-mour specimens ex-cluded)	676/769	VI (no algo-rithm) In-per-son (sin-gle ob-server)	Subjec-tive im-pression; defi-nitely malig-nant	Derma-tolo-gists; n = 25 Board-certified	Histol-ogy MM 4; MiS 4 BCC: 110; cSCC: 20 "Be-nign" di-agnoses: 595 152/ 769; 20%	Poor-qual-ity index test im-age mis-regis-tered or poor-quality im-ages (un-focused or con-taining a motion artifact)
Ek 2005	NC P-CS Australia Special-ist clinic	Lesions excised for which malignancy could not be ex-cluded	1223/2582	VI (no algo-rithm) In person	Subjec-tive im-pression	Plastic surgeon (n = 4 or 5; mixed experi-ence; 3 consul-tants, 1 plastic	Histol-ogy MEL 23 BCC 1214; SCC 517; BD 188; SK 63; 577	Incom-plete or incor-rectly entered profor-mas were ex-cluded -

(*Continued*)

						surgery trainee (usually 1st year, on 6-month rotation) and a clinical assistant) Unclear	other benign (including 330 solar keratosis) 1754/2582; 68%	79 participants with 96 lesions
McGovern 1992	WPC-algs P-CS USA Community	PSL (> 10 mm) excised to rule out dysplasia, MiS or MM	179/237	VI (7-point; (A) BCD) In-person; single	7-point: ≥ 2, ≥ 3, ≥ 4 characteristics present (A) BCD: ≥ 1, ≥ 2, ≥ 3 characteristics present	NR (presume dermatologist) experience. NR	Histology MM 6; MiS 6 BCC 4; SK 32; BN 138; AK 6; other 45 15/192; 8%	32 lesions unaccounted for; 13 excluded due to lesion size of ≤ 8 mm. 192 evaluated for ABCD and 3-point; 205 evaluated for 7-point
Stanganelli 2000	WPC R-CS Italy Specialist clinic	PSL referred by dermatologists and GPs either for pre-surgical assessment or consultation	NR/3372	VI (ABCD) Dermoscopy (no algorithm) In person (single)	NR Subjective impression	NR (assumed dermatologist - described as one of the co-authors; n = 1)	Histology/registry FU MEL 55 BCC 43; BN 3274 98/3372; 3%	None reported
Steiner 1987	P-CS Austria Special-	Small (< 10 mm) diagnostically equivocal PSL; no absolute	NR/318	1. VI (no algorithm)	Subjective impression	Dermatologists (n = 3;	Histology MM 49;	None reported

(*Continued*)

	ist clinic	agreement on clinical diagnosis among investigating clinicians at a PLC		2. Dermoscopy (pattern) In person		high experience - "experienced dermatologists") Consensus diagnosis of 3 observers	MiS 24 BCC 20 BN 143; SK 20; lentigo simplex and nevoid lentigo 19; other 15 93/318; 29%	
Walter 2012	BPC RCT UK Primary	Any suspicious PSL that could not immediately be diagnosed as benign	654/792 (control arm only)	VI (7-point) Siascope (iv arm) In person (single)	NR	GP (n = 28) Nurse practitioner (n = 2) Low (excluded if specialist dermatology training)	Histology/ clinical FU (3-6 months) /expert dx Control group only: MM 16; MiS 2 BCC 4; SK 20; DF 2; lentigo 5; "benign" 686; unknown 10 22/773; 3%	19 (5 due to violation of recruitment criteria or discontinued protocol; 1 died; 4 did not attend for dermatology assessment; 2 missing histology; 7 not clearly accounted for)	
Image-based									
Carli 2002b	WPC R-CS Italy Secondary	Clinically suspicious or equivocal PSL	NR/57	1. VI (NR) 2. Dermoscopy (NR)	NR	Dermatologists (n = 2) Image-based;	Histology MM 6, MiS 5 BCC 10	4 'not evaluables' excluded (1 MM,	

(*Continued*)

		undergoing excision for diagnostic purposes; all ≤ 14 mm diameter				high experience ("with experience in the field of PSL"); consensus of 2	BN 31, SK 1; other 4 20/54; 37%	3 benign)
Rosendahl 2011	NC R-CS Australia Primary	PSL submitted for histology from the primary care skin cancer practice of one study author	389/463	1. VI (no algorithm) 2. Dermoscopy (pattern)	1. Subjective impression 2. Both characteristics present	Dermatologist (n = 1) Image-based; high experience (confirmed by study author); single observer	Histology MM 9; MiS 20 BCC 72; SCC 5 BN 217; BD 18; AK 14*; BNM 140 *considered malignant by study authors 104/463; 22%	3 poor-quality images excluded
Stanganelli 1998a	WPC R-CS Italy Training images	PSL images selected from computerised files of the skin cancer clinic	NR/30	1. VI (no algorithm) 2. Dermoscopy (no algorithm)	NR	Dermatologists (n = 20) Image-based; experience NR ("experience in ELM but (with) no formal training"); average	Histology MEL 10 BCC 4 BN 10, SK 3, other 3 14/30; 47%	None reported

(*Continued*)

AK: actinic keratosis; **BN**: benign naevi; **BCC**: basal cell carcinoma; **BD**: Bowen's disease; **BP**C: between person comparison (of tests); **CCS**: case control study; **CS**: case series; **cSCC**: cutaneous squamous cell carcinoma; **DF**: dermatofibroma; **FU**: follow-up; **dx**: diagnosis; **ELM**: epiluminescence microscopy; **GP**: general practitioner; **MEL**: invasive melanoma or atypical intraepidermal melanocytic variants; **MiS**: melanoma in situ (or lentigo maligna); **MM**: malignant (invasive) melanoma; **NC**: non comparative; **NR**: not reported; **P**: prospective; **PCP**: primary care practitioner; **PLC**: pigmented lesion clinic; **PSL**: pigmented skin lesion; **R**: retrospective; **RCT**: randomised controlled trial; **SCC**: squamous cell carcinoma; **SK**: seborrhoeic keratosis; **SN**: Spitz naevi; **VI**: visual inspection; **WPC**: within person comparison (of tests); **WPC-algs**: within person comparison of algorithms

CONTRIBUTIONS OF AUTHORS

JD was the contact person with the editorial base.

JD co-ordinated contributions from the co-authors and wrote the final draft of the review.

SB conducted the literature searches.

JD, NC, LFR, DT, KYW, RBA, RA, and MF screened papers against eligibility criteria.

JD and NC obtained data on ongoing and unpublished studies.

JD, NC, LFR, DT, KYW, RBA, RA, and MF appraised the quality of papers.

JD, NC, LFR, DT, KYW, RBA, RA, and MF extracted data for the review and sought additional information about papers.

JD entered data into Review Manager 5.

JD, MJG and JJD analysed and interpreted data.

JD, JJD, NC, LFR, YT and CD worked on the methods sections.

JD, FW, DT, KYW, RBA, RA, MF, RNM and HCW drafted the clinical sections of the background and responded to the clinical comments of the referees.

JD, JJD, CD and YT responded to the methodology and statistics comments of the referees.

KG was the consumer co-author and checked the review for readability and clarity, as well as ensuring outcomes are relevant to consumers.

JD is the guarantor of the update.

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DECLARATIONS OF INTEREST

Jacqueline Dinnes: nothing to declare.

Jonathan J Deeks: nothing to declare.

Matthew J Grainge: nothing to declare.

Naomi Chuchu: nothing to declare.

Lavinia Ferrante di Ruffano: nothing to declare.

Rubeta N Matin: "my institution received a grant for a Barco NV commercially sponsored study to evaluate digital dermoscopy in the skin cancer clinic. My institution also received Oxfordshire Health Services Research Charitable Funds for carrying out a study of feasibility of using the Skin Cancer Quality of Life Impact Tool (SCQOLIT) in non melanoma skin cancer. I have received royalties for the *Oxford Handbook of Medical Dermatology* (Oxford University Press) and payment from the UK Photopheresis Society for a lecture on cutaneous graft versus host disease (October 2017). I have no conflicts of interest to declare that directly relate to the publication of this work."

David R Thomson: nothing to declare.

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Susan E Bayliss: nothing to declare.

Yemisi Takwoingi: nothing to declare.

Clare Davenport: nothing to declare.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We set out to review visual inspection and dermoscopy for the detection of melanoma in a single review; however, due to the volume of evidence identified, we prepared two separate reviews: one for visual inspection alone and one for dermoscopy, the latter including direct comparisons with visual inspection where the same studies evaluated both tests.

We changed the primary objectives and primary target condition from detection of cutaneous invasive melanoma alone, to the detection of cutaneous invasive melanoma and atypical intraepidermal melanocytic variants, as the latter is more clinically relevant to the practicing clinician. We included the detection of the target condition of invasive melanoma alone as a secondary objective instead.

We tailored secondary objectives to the individual test, and added two objectives, to determine the diagnostic accuracy of individual algorithms for visual inspection, and to determine the effect of observer experience.

Sources of heterogeneity that could be investigated (as listed under Secondary objectives) were restricted due to lack of data.

We amended the text to clarify that studies available only as conference abstracts would be excluded from the review unless full papers could be identified; studies available only as conference abstracts do not allow a comprehensive assessment of study methods or methodological quality.

We excluded, rather than included, studies using cross-validation, such as 'leave-one-out' cross-validation, as these methods are not sufficiently robust and are likely to produce unrealistic estimates of test accuracy.

To improve clarity of methods, we replaced this text from the protocol, "we will include studies developing new algorithms or methods of diagnosis (i.e. derivation studies) if they use a separate independent 'test set' of participants or images to evaluate the new approach. We will also include studies using other forms of cross validation, such as 'leave-one-out' cross-validation (Efron 1983). We will note for future reference (but not extract) any data on the accuracy of lesion characteristics individually, e.g. the presence or absence of a pigment network or detection of asymmetry" with, "studies developing new algorithms or methods of diagnosis (i.e. derivation studies) were included if they:

- used a separate independent 'test set' of participants or images to evaluate the new approach, or
- investigated lesion characteristics that had previously been suggested as associated with melanoma and the study reported accuracy based on the presence or absence of particular combinations of characteristics.

Studies were excluded if they:

- used a statistical model to produce a data driven equation, or algorithm based on multiple diagnostic features, with no separate test set.
- used cross-validation approaches such as 'leave-one-out' cross-validation (Efron 1983)
- evaluated the accuracy of the presence or absence of individual lesion characteristics or morphological features, with no overall diagnosis of malignancy
- reported accuracy data for 'clinical diagnosis' with no clear description as to whether the reported data related to visual inspection alone
- were based on the experience of a particular skin cancer clinic, where dermoscopy may or may not have been used on an individual patient-basis."

Although we extracted any reporting of special interest or accreditation in skin cancer according to observer expertise, we were unable to analyse the effect on accuracy.

We proposed to supplement the database searches by searching the annual meetings of appropriate organisations (e.g. British Association of Dermatologists Annual Meeting, American Academy of Dermatology Annual Meeting, European Academy of Dermatology and Venereology Meeting, Society for Melanoma Research Congress, World Congress of Dermatology, European Association of Dermato Oncology), however due to volume of evidence retrieved from database searches and time restrictions we were unable to do this.

For quality assessment, we further tailored the QUADAS-2 tool according to the review topic. In terms of analysis, due to lack of data we did not restrict analyses to per-participant data only, nor perform sensitivity analyses as planned.